SPLIT-COURSE HYPOFRACTIONATED RADIOTHERAPY FOR PALLIATION OF ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

A SINGLE ARM PROSPECTIVE STUDY

INSTITUTION

DEPARTMENT OF RADIOTHERAPY, BIRO

MADRAS MEDICAL COLLEGE

RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL

CHENNAI -600 003.

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF

MD BRANCH IX RADIOTHERAPY

EXAMINATION APRIL 2015

The Tamil Nadu Dr. M.G.R Medical University

Chennai - 600032

CERTIFICATE

This is to certify that **Dr. MANIK VISHAL DEVKISHEN** has been a Post Graduate MD Student during the period from May 2012 to April 2015 in the Department of Radiotherapy, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai.

This dissertation titled "**SPLIT-COURSE HYPOFRACTIONATED RADIOTHERAPY FOR PALLIATION OF ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA**" is a bonafide work done by him during his study period and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfilment of the MD Branch IX Radiotherapy examination.

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ACKNOWLEDGEMENT

I thank **Lord**, for providing me with the perseverance and patience required to complete this study.

I express my sincere gratitude to **Prof. Dr. R. VIMALA, M. D.,** Dean, Madras Medical College, Chennai - 03, for being a commendable source of encouragement. I am thankful to her for permitting me to conduct this study.

I express my sincere gratitude to **Prof**. **Dr. KALAISELVI., M.D**., Vice Principal, Madras Medical College, Chennai – 03 for her kind words of advice.

I express my gratitude to Chairman **Prof. Dr. C. RAJENDRAN, M.D.,** and the members of the Institutional Ethics Committee, Madras Medical College and Rajiv Gandhi Govt. General Hospital, Chennai - 03, affiliated to The Tamil Nadu Dr. M. G. R Medical University, Chennai - 32 for having approved my study.

I express my gratitude to **Prof. Dr. M. VANITHA, M. D**., Director, Barnard Institute of Radiology and Oncology, Madras Medical College and Rajiv Gandhi Govt. General Hospital, Chennai – 03, for her subtle words of encouragement.

I am extremely grateful to **Prof. Dr. S. SHANMUGAKUMAR, B. Sc., M.D, D.M.R.T.**, Professor& Head, Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai - 03 for his out of the box questions, which made us to ponder over the often neglected basics of medicine and oncology. The OPD and bed side clinics, classroom discussions have been immensely helpful.

I am gratified to **Prof. Dr. N. V. KALAIYARASI, M.D.,** Additional Professor**,** for her untiring support and advice related to this study and otherwise. Her constant reminders regarding regular readings. And for her guidance regarding all the practical issues that we face in our daily practice.

I am extremely thankful to **Prof. Dr. P. BALASUBRAMANIAM, M.D., D.M.R.T.**, Ex- Additional Professor. He was the constant source of encouragement, right from the very beginning of the course for selecting thesis topics, taking part in research activities. He also proved to us that age is just a number, as his energy and enthusiasm were unmatched. His constant will to question us during ward rounds, encouraged us to study further.

I am grateful to **Prof. Dr. MUTHUVEL**, Professor& HOD, Department of Radiological Physics, for his support and guidance regarding the physics aspects of radiotherapy and planning.

I wish to express my sincere gratitude to all the Assistant professors of our department (past and present) for guiding me during my study period. They helped me in acquiring and selecting the cases, planning the treatment, executing the planned radiotherapy, manage the side effects.

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Dr. C. SUNDARESAN, M.D.R.T

Dr. ARUN RAMANAN, M.D.R.T

Dr. MADHARSHAH, D.M.R.T

I am grateful to the Medical Physicists of the Department of Radiological Physics who helped me plan the radiotherapy and offered guidance during difficult

situations and dose calculations, **Mr. THIRUMAVALAVAN and Mrs. A. KOPPERUNDEVI.**

My words of appreciation and gratitude go out to the radiographers **Mr. PURUSHOTTAM, Mr. VIVEK, Mr. GABRIEL** and their team of student radiographers for their sincere execution of the treatment, kind support and service rendered for the patients in this study.

I am grateful to **Prof. DR. JAGDISH CHANDRA BOSE**, M.S., M.Ch, Professor and Head, Department of Surgical Oncology, and **PROF. DR. K. KALAICHELVI**, M.D., D.M, Professor and Head, Department of Medical Oncology, for their appropriate guidance whenever approached.

My sincere gratitude goes out to my fellow post graduates, especially Dr. Rajmane P., Dr. A. Ramya, Dr. Aoakhum Kichu for being with me whenever I needed help and moral support.

I am also thankful to my family and 'Bhai' for his continuous support and enduring all the difficulties throughout my post-graduation. I thank my fiancé,

Dr. Prachi Sharma for pulling the best out of me during the tough periods when everything felt in correct.

Lastly and most importantly, I wish to acknowledge the co-operation of my patients during the study period without whom this study would have not been impossible.

DECLARATION

I solemnly declare that the dissertation titled "**SPLIT-COURSE HYPOFRACTIONATED RADIOTHERAPY FOR PALLIATION OF ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA**",a SINGLE ARM PROSPECTIVE STUDY was done by me at the Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during **March 2014 to August 2014** under the guidance and supervision of Prof. Dr. S.SHANMUGAKUMAR.

The Dissertation is submitted to The Tamil Nadu Dr. M. G. R. Medical University towards the partial fulfilment for the award of M.D. Degree (Branch IX) in Radiotherapy.

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CONTENTS

SPLIT-COURSE HYPOFRACTIONATED RADIOTHERAPY FOR PALLIATION OF ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

Dr. Vishal Manik*, Prof. Dr. S. Shanmugakumar, Prof. Dr. N. V. Kalaiyarasi

INTRODUCTION: A significant proportion of patients with head and neck squamous cell carcinoma (HNSCC) are unsuitable for radical treatment due to factors including tumour stage, performance status (PS) and co-morbidity. Palliative radiotherapy has a useful role in the control of local symptoms.

AIM: To assess the local symptom control of advanced HNSCC treated with split course hypofractionated radiotherapy. Additionally, to assess the Quality of Life (QoL); the acute toxicity to the treatment and the immediate loco-regional response.

MATERIALS AND METHODS: Thirty patients of very advanced HNSCC with PS of >2 were selected. All the patients after basic work up, were planned to receive initial course of 20Gy radiation (4Gy/ 5 fractions) followed by a two week gap and then re-assessment. All patients with absent or manageable toxicity were further treated with one more course

of 20 Gy radiation. Symptom relief was assessed before and after each course of radiation. QoL was assessed using the EORTC QoL questionnaire, before and after radiotherapy.

RESULTS: Out of the study population, 70% were males, 50% belonged to age group 61-70 years and all had a PS ≥3. Oropharynx (33.3%) was the commonest site with base of tongue (20%), the commonest subsite. Stage grouping was IVB in 56.67% with 46.67% having a N3 node and dysphagia (43.3%) at presentation. Only 3 patients could not complete the planned courses of RT. Good symptom relief was observed in 73.3%. Improvement in symptom scales was seen, however, functional and global health scores remained low. None had more than Grade 1-2 toxicity from first course. Grade 2 toxicity was seen in majority of patients after second course. Overall response rate was 100% with partial response (PR) in most cases. Median duration of response was 2 months post-treatment.

CONCLUSION: Split course hypofractionated palliative RT is feasible in advanced HNSCC and allows for shorter treatment time with acceptable symptom relief.

KEY WORDS: Split – course, Hypofractionation, Palliation, Advanced HNSCC

INTRODUCTION:

Cancer, a disease which has perplexed many, doctors and patients alike is now one of the leading causes of death worldwide. Complex aetiology, genetic and molecular interplay, social and lifestyle factors, have been responsible for difficulties in diagnostics and treatment of this dreaded disease.

1. Cancer Epidemiology:

The specialized cancer wing of the World Health Organization, International Agency for Research on Cancer (IARC), released the latest data on cancer incidence, mortality, and prevalence worldwide in December 2013. Their online database, GLOBOCAN 2012, revealed the most recent estimates of incidence and prevalence rates of different types of cancer. It estimated that 14.1 million new cases of cancer and 8.2 million cancer-related deaths occurred in 2012, compared to 12.7 million and 7.6 million, respectively, in 2008.[1] Prevalence estimates for 2012 showed that there were 32.6 million people surviving with a cancer diagnosed in the previous five years.[2] Over half of all cancer incidence (56.8%) and cancer mortality (64.9%) in 2012 occurred in the developing nations. Cancer and related issues have always occupied a

distinctive stature in the Indian oncologic scenario. With westernisation of our culture, habits and lifestyle practices, Indian population has seen an upward trend in the incidence of cancer over the past two decades. In India, an estimated 5.5 lac people died of cancer in 2010. [3] According to a recent Government of India study, 7% of all deaths annually, occur owing to cancer. Though the incidence has gone up, the mortality rates have not reduced either thus increasing the overall cancer burden over the society. Further, in the recent years, figures have shown a gradual increase in the incidence among younger age groups due to use of some form of tobacco among school children in age group of 10-15 years. [4]

2. Head & Neck Cancer Statistics:

All over the world, head and neck cancers account for more than 550,000 cases annually. [5] Overall, 57.5% of global head and neck cancers occur in Asia especially in India, for both sexes. [6] In the developed countries, head and neck squamous cell carcinoma (HNSCC) account for only 3% of all malignancies. [7] Oral cavity and tongue cancers are more common in India while pharyngeal and laryngeal cancers are more common in other populations. [8] Lip and pharynx were found to be the commonest sub-sites in Indian patients. [3] Here,

head and neck cancers are the second most common cancer in males and fourth most common cancer in females. [9]

3. Aetiology:

Though cancer pathogenesis is an interplay of various factors including molecular genetics, environmental and lifestyle, tobacco in any form, alcohol and Human Papilloma Virus (HPV) infection have been the established risk factors for development of head and neck squamous cell carcinoma.

a. Tobacco: Tobacco-related cancers represent around 42% of male and 18% of female cancer deaths in India. [3] Tobacco may be consumed either in the form of smoking or in smoke-less form.

Smoking: Tobacco smoking can be in the form beedi, hookah, cigarettes, reverse smoking and cigars has been found to be an independent risk factor in 85-90% of the patients. [10-12] Cigars are the most dangerous with tobacco content equivalent to that of two and a half cigarettes. Tobacco smoking in various studies has shown a strong association with aero-digestive tract tumours with risk escalation of about 5 to 25-fold among smokers compared to never smokers. [13] Ten years after quitting, the risk of a smoker is reduced

by 50%. [12] Head and neck cancer patients who receive radiation treatment and yet continue to smoke have a lesser likelihood of achieving a complete response. [14]

Smokeless tobacco: Smokeless tobacco can be in the form of gutkha, khaini, zarda, mixed with pan and lime. Practice of chewing tobacco quid and placing it in the gingivo-buccal sulcus develops a chronic local irritation and over time leads to carcinogenetic changes.

Paan Masala: Paan Masala with its various flavouring and additive compounds consisting of nitrosamines and phosphates was the most dangerous compounds. Various studies have shown that chewing pan masala can develop cancer within a very short lead time as compared to tobacco. Also its easy availability has caused a spike of head and neck cancer among very young age groups. Thus, the ban on sale of these products in 2013 was a welcome move by the government.

Areca/ Betel Nut: WHO in a recent statement declared areca nut chewing as a potential of oral pre-malignant lesions and

carcinogenesis. Areca nut is commonly used in paan, mukhwaas (an Indian after meal mouth freshener).

b. **Alcohol:** Alcohol by itself has shown to increase the risk of head and neck cancer by fivefold. [15] Along with tobacco it has a synergistic action in carcinogenesis. [16] A meta-analysis of 26 studies that analysed effects of alcohol showed a relative risk of 1.85-6.01 based on the quantity of alcohol consumed daily. [17] Oral cavity and pharynx are the sites most exposed during alcohol/ tobacco intake and hence these sites show an increased propensity to develop a primary tumour.

c. **HPV Infection:** HPV infection with serotypes 16 and 18 have been associated with head and neck cancer, most commonly, oropharyngeal tumours. [18-20]These infections are mostly acquired due to increase in unnatural or risky sexual behaviour patterns. Risk factors include high lifetime vaginal or oral sex partners, sero-positivity for HPV-16 viral capsid protein antibodies. HPV-16 is the most common serotype and positivity is observed in 60-90% of the oropharyngeal cases. A meta-analysis of all studies which assessed the relation between HPV infection and head and neck cancers

showed an improved Overall Survival (OS) and Diseases Free Survival (DFS) among oropharyngeal tumours that showed HPV infection positivity. [21] In the re-analysis of RTOG 0129 study, HPV status was independently associated with improved outcomes. HPV positive tumours have shown to have better prognosis regardless of the treatment modality utilised.

d. Dietary Factors: Diet low in fibre, fresh fruits, vegetables and source of anti-oxidants, increased consumption of red meat and fatty diet have been associated with risk of aero digestive malignancies.

4. Molecular Biology:

Case-control studies have shown that first degree relatives of patients with head and neck squamous cell carcinoma have a 3.5 to 3.8 fold risk of developing HNSCC themselves. [22] Thus this hints towards underlying genetic mechanisms leading to carcinogenesis. Carcinogenesis of head and neck tumours results from multiple genetic and epigenetic alterations of molecular pathways in the squamous epithelium. The following signalling pathways have been implicated in HNSCC.

A. **P16/ p53/ Cyclin D:** P16 is an inhibitor of cyclin-dependent kinase (CDK), which is required in G1 cell-cycle regulation. Loss of p16 protein has been observed in most advanced premalignant lesions and appears necessary for immortalization of keratinocytes.[23] Inactivation of p53 is the most common genetic change in all of human cancer. [24] Role of p53 is to halt cell-cycle progression if there is DNA damage and induce apoptosis with inadequate DNA repair. Mutations of p53 result in a progression from pre-invasive to invasive lesions. The prevalence of p53 mutations is greater in patients who smoke and drink alcohol, thus establishing the causal role of these carcinogens. Further, constitutive activation of oncogene cyclin D1 has been shown to confer a growth advantage in HNSCC. [25] Other tumour suppressor genes, including Rb and p16, are negative regulators of the cyclin D1 pathway and often are inactivated in human neoplasms. Cyclin D1 amplification is independent of p16 inactivation in head and neck cancers. [26]

B. **PI3-K/ AKT/ mTOR:** Mutation in the PI3-K pathway are seen in many human cancers and activation of PI3/ AKT/ mTOR pathway has been associated with carcinogenesis of the head and neck tumours. [27] PI3-K mutations bring about drug resistance, growth

advantage and transforming capacity. [28] PI3-K are activated by tyrosine kinase inhibitors including EGFR and oncogenic proteins that results in subsequent phosphorylation and subsequent activation of AKT. PI3-K also brings about activation of mammalian target of rapamycin (mTOR), which in turn activates a kinase that regulates protein synthesis.

C. **Epidermal Growth Factor Receptor (EGFR):** EGFR is a receptor tyrosine kinase from the ErbB family of cell surface receptors. Once activated it can signal via the MAPK, Akt, ERK and Jak/ STAT pathways which are related to cellular proliferation, invasion, angiogenesis, metastasis and apoptosis. [29] Almost 80-90% of the HNSCC have dysfunction of EGFR receptor and its related pathways. [30] Elevated levels of EGFR expression confer a worse disease free and cause-specific survival. [31] Thus, strategies and molecules have been formed to target the EGFR pathway like tyrosine kinase inhibitors (TKIs) and monoclonal antibodies. Cetuximab is one of the vastly studied monoclonal antibody against EGFR which has shown to improve overall survival and duration of loco-regional control. [32] It has been approved by US-FDA for use

in HNSCC. Other agents like TKI Gefitinib and Erlotinib have not shown any survival advantage in the similar setting. [33]

D. Human Papilloma Virus (HPV): HPV is a double stranded circular DNA virus with affinity for squamous epithelium. [34] Over expression of the E6 and E7 oncoproteins contained in the viral genome disrupt the function of tumour suppressor Rb and p53 genes which in turn results in carcinogenesis. [35] HPV positive tumours have shown to have poorly differentiated and basaloid histology frequently. It has also been shown that human epithelial cells expressing E6 and E7 genes from HPV-16 become immortal. [36]

5. Clinical Presentation:

Almost all the patients will present with a common symptom of nutritional insufficiency that is loss of appetite and loss of weight along with other long standing constitutional symptoms. The other symptoms at presentation are usually specific to the site of primary tumour. Oral cavity lesions present with an ulcero-proliferative or indurated lesion over the tongue/ lip/ buccal mucosa/ palate. The lesion might be associated with pain which might be aggravated by food intake. In

oropharynx and hypopharynx, the usual presenting symptom is dysphagia or majority might even present with cervical lymph adenopathy in absence of symptoms from the primary. The growth or cervical lymph nodes might cause secondary symptoms by mass or pressure effect on neighbouring structures in the form of pain, breathlessness or stridor. Laryngeal primaries are usually detected early in their course because of prominent symptom in the form of hoarseness of voice. Some cases of advanced primaries might present with bleeding or severe stridor accounting as pure oncologic emergencies.

6. Prognostic and Predictive Factors:

Various literature reviews and trial data have established the following prognostic factors in cancer of head and neck.

A. Tumour Size: The T stage in TNM is one of the most important prognostic factor which can affect the prognosis. The local control rates and survival rates are seen to diminish with advancing T stage. Tumour thickness and depth of invasion increase the risk of regional metastases. [37]

B. Nodal Stage: Cervical lymph node metastases is one of the most significant predictor of outcome. [38] Patients with positive cervical lymphadenopathy have their 5 year survival rates reduced by 50%. [39] Multiple levels of lymph node positivity or Extra-capsular extension (ECE) worsen the prognosis further. [38]

C. Tumour Site: Cancer of larynx has better prognosis compared to oral cavity, oro and hypopharynx. This can be attributed to pathways of tumour spread and lymphatic network of that particular site (Glottis has sparse lymphatics compared to other sites which have a dense lymphatic drainage).

D. Miscellaneous Factors: Peri-neural invasion, lympho-vascular invasion, post-operative margin status have also shown prognostic implications in various studies. Histologic Grading has not been established as an independent prognostic factor due to wide variations in its pathologic interpretation. [37]

7. Treatment Synopsis:

Ideal management for locally advanced head and neck cancer is a multi-modality approach incorporating all three disciplines of oncology namely surgery, radiation and chemotherapy. For early stage cancer, it can be either radiation or surgery, both giving equivocal local control rates at most of the sites. The choice largely depends on the primary physician and the patient's preference. Locally advanced lesions are technically difficult to operate upon, hence, concurrent chemoradiation forms the definitive choice for such patients. Though the toxicity of such combined modality treatment is much higher compared to radiation or surgery alone, randomized controlled trials have shown that most of the toxicities are manageable and tolerable and that the combined treatment helps to achieve a higher cure rate compared to radiation alone. Failures after concurrent chemoradiation and those with residual disease can be taken up for salvage surgery.

A. Principles of Surgery: All cases of head and neck cancer should be examined by an experienced head and neck cancer surgeon to assess the resectability. Surgery is the definitive modality where by the entire tumour can be removed en block along with a comprehensive

neck dissection. Neck dissection would be ipsilateral in well lateralized lesions. For lesions crossing the midline or primary sites having bilateral drainage, a bilateral neck dissection should be performed. In a node negative case showing deeper invasion of the primary, neck dissection is only elective and hence a selective dissection can be performed while preserving the major structures. In cases that the surgeon feels can be technically challenging or where complete resection is doubtful, may be taken up for concurrent chemo-radiation. The terms resectable and unresectable have been replaced by moderately advanced and very advanced as the tumour is never unresectable. It is either that the surgeon feels technically, the clearance would not be adequate or the patient is medically unfit for surgery. Surgery enables to examine the histopathology of the tumour upfront without any radiation induced alteration in tissue. It also enables to reserve radiation for any adverse pathological feature seen in the post-operative specimen. Reconstructed tissues and grafts heal up well prior to radiation than in an irradiated case as the local micro vascular changes do not occur.

B. Principles of Systemic Therapy: The landmark data from meta-analysis of various trials of chemotherapy in head and neck cancer (MACH-NC)[40] has shown that concurrent chemotherapy gives an absolute benefit of 6% compared to radiation alone. Single agent Cisplatin (D_1-D_{22}-D_{43}) is the standard regimen for all head and neck cancer cases planned for concurrent chemoradiation. No added advantage was seen with Cisplatin combination chemotherapy along with radiation. No other drug in single agent setting showed benefit similar to Cisplatin. Hence NCCN Guidelines recommend under category 1, only single agent Cisplatin as the standard regimen in concurrent setting. Further, induction chemotherapy has shown an overall survival benefit of about 2%. Induction with 2-3 cycles using three drug regimen of taxol, platinum and 5-flurouracil has shown superiority over two drug regimen in the form of PF. The benefit of induction is seen most in hypopharynx followed by oropharynx and least in larynx and oral cavity. However, in the paucity of data, NCCN favours the use of induction chemotherapy only as a category 3 recommendation i.e. there is a major disagreement towards its use.

C. Principles of Radiation Therapy: Radiation in early stage HNSCC can be delivered either in the form of tele therapy or brachytherapy or combined with tele therapy followed by a brachytherapy boost. Advantages of radiation are that the functional and anatomic structure of the involved tissue is maintained and hence the morbidity of treatment is low. With incorporation of concurrent chemotherapy, many locally advanced cases can achieve a good local control along with organ preservation. Newer techniques like 3D-Conformal and intensity modulated radiation therapy help in minimising the adjacent normal tissue doses and consequential toxicity while at the same time allow for dose escalation at the tumour which may transform into an improved local control. When chemoradiation is the definitive modality, all at-risk cervical lymph node stations are to be incorporated into low-risk, intermediate-risk or high-risk CTVs (Clinical Target Volume). The dose prescription will vary depending on the risk category from 44-66 Gy. When given post-operatively, the indications for Adjuvant radiotherapy are advanced T stage, multiple levels of lymph node positivity, peri-neural and Lymphovascular invasion. Chemotherapy is added to post-operative radiation in cases of margin positivity and extra

capsular extension (ECE).Radiotherapy is generally given in fractions. The different types of fractionation are:

Conventional: Dose fractions of 1.8-2.2 Gy are considered to be conventional. These are the usual recommended dose fractions under various guidelines of cancer treatment. For head and neck cancer, the total dose should be 66 – 70 Gy, in 2.2 to 2 Gy fractions respectively.

Altered Fractionation: It can be of following types:

i. **Accelerated**: Decreases the overall treatment time to counter the accelerated repopulation in tumour cells during the treatment. Improves loco regional control.

ii. **Pure accelerated:** Decreases the overall treatment time without altering the total dose or fractionation.

iii. **Hybrid accelerated:**

    1. **Type A:** Reduced total dose along with reduced overall treatment time.

2. **Type B:** Reduced treatment time, total dose unchanged and is given over two-split courses.
3. **Type C (accelerated concomitant boost):** Total dose unchanged, overall treatment time reduced with concomitant boost delivered as a second daily dose, given at least 6 hours apart.

iv. **Hyper fractionated Radiotherapy:** Total dose is increased while the dose per fraction is significantly reduced and the number of fractions are increased so as to deliver more than 5 fractions a week. The overall treatment remains largely unchanged.

Brachytherapy: No radiotherapy discussion in head and neck cancer is complete without addressing the principles of brachytherapy. The unique advantage of this mode of treatment is that high dose can be delivered directly into the target tumour tissue with minimal spillage of the dose into the surrounding normal tissue. Thus, in spite of proton therapies and other modern conformal techniques, brachytherapy is also regarded as

the highest degree of conformal therapy. Brachytherapy can be delivered using following techniques:

a. **Surface/ mould applicators:** For lip and buccal mucosa lesions which are accessible externally.
b. **Interstitial implants:** These are applied for lesions of tongue and soft palate which are infiltrative or diffuse.
c. **Intra-cavitary applicators**: These can be used for optimal dose delivery for pharyngeal lesions where surface or interstitial implantation is not possible.

The usual isotopes used for High Dose Rate (HDR) treatment are $Ir^{192}$and Co^{60}. The recommended fractionation is 3 Gy for HDR application, to a total dose of 21 Gy for boost when used after tele-therapy of 45-50 Gy. When using it as a sole therapy in early stage lesions, fractions of 3-6 Gy to a total dose of 45-60 Gy are recommended. Brachytherapy can be a useful technique in cases of recurrent/ advanced disease where surgery or re-irradiation with substantial doses of external beam radiation are not feasible by providing good tumour control and symptom relief.

Precautions specific for brachytherapy treatment delivery:

a. Space between adjacent interstitial implants should be at least 1 cm to provide homogenous distribution in the entire tumour
b. Proximity to jaw or other bones should be more than 1 cm to reduce the risks of osteoradionecrosis.
c. CT based delineation of treatment volume to plan the number of interstitial catheters required for homogenous dose coverage.
d. Other surgical precautions such as normal bleeding/ clotting profile, anaesthetic fitness apply.

Mandatory precautions prior to external beam radiation of head and neck:

i. **Dental evaluation and management:** Xerostomia and salivary gland dysfunction are the major side effects after any head and neck irradiation. These side effects drastically increase the risk of dental sequelae such as caries, alveolar infection and eventually osteoradionecrosis (ORN). Radiation

also increases the risk of demineralisation by directly damaging the dental tissue. Radiation related caries and tissue changes may appear within first few months post treatment. [41, 42] Risk should be assessed for caries and periodontal disease. All potential sources of infection should be eliminated. Any dental extractions, should be performed at least 2 weeks prior to initiation of radiation therapy. Topical fluoride may be added for daily use if risk of caries is high. Regular rinsing of mouth with commercially available solutions or using home-made solutions of salt and soda bicarbonate in water.

ii. **Nutritional Management:** Patients with head and neck cancer are prone to weight loss result of their disease process per se, health patterns and treatment related toxicity. Management of nutritional intake is as essential as the therapy itself because studies have shown its influence on outcome and complications. Prophylactic feeding procedure is not recommended in patients with a good performance status, no signs of significant pre-treatment weight loss, airway obstruction or severe dysphagia/ dehydration.

iii. **Metallic implants/ accessories:** Patients should be asked to remove all metallic accessories such as gold ornaments or ear/ nose rings. Those with metallic implants in the irradiated area should be planned for radiotherapy prior to surgery or should be monitored carefully for early toxicities, if radiation cannot be avoided. Photons from the radiation beam are prone to produce scatter electrons on interaction with metal surfaces. These secondary electrons, having a lower depth of penetration, remain confined to the skin and subcutaneous tissues thus giving rise to a dose augmentation and increased local toxicity.

D. Principles of Palliation: Palliation is often described as "to cure sometimes, to treat often, comfort always". The term "palliative" is conventionally used to describe strategies for patients in whom "cure" is a distant option because of disease or patient related factors. According to All India Institute of Medical Sciences data, 70% of head and neck cancer present in advanced stages where cure is difficult to achieve. [43] Palliation can be delivered using a single modality of treatment which relieves the symptoms to the maximum and at the same time does not add to toxicity or morbidity. Hence, it

can be a debulking surgery to remove a huge fungating neck nodal mass to relieve pressure effects and discomforting smell. Or it can be radiation, usually short course and hypofractionated targeted to symptomatic primary/ nodal mass for relieving symptoms and at the same time avoiding patient discomfort that accompanies a protracted course. Chemotherapy also has a role in palliation of some solid tumours, less frequently in head and neck, and in cases where extent/ systemic spread or performance status rules out the use of other modalities.

8. Very Advanced Lesions:

Even with robust screening and patient awareness programs, the head and neck cancer cases present in our day to day practice more often in the advanced stage. The various psychosocial factors which lead to delay in diagnosis and seeking treatment include beliefs like ‘cancer a curse’, ‘trivial ulcers in the mouth are benign’ and also the fear that ‘the prolonged treatment will affect the family’. [44] Sometimes delay occurs between diagnosis and initiation of treatment due to futile advice from relatives to try local remedies and avoid expensive and morbid cancer treatment. With advanced nature of lesions, the

performance status, age, willingness of patient to undergo aggressive toxic treatment and many other factors come into play. Young patients with good performance status and very advanced lesions can be taken up for concurrent chemoradiation and may be followed up with surgery for taking care of the residual disease. Induction chemotherapy may be tried but trials are yet to show any substantial improvement in survival benefit. Practically, even with advances in chemotherapeutic drugs, molecular targeted therapies and radiation techniques, the benefits in loco-regional disease control or survival have not increased as drastically as desired for these sub group of patients. Poor performance status of patients with very advanced disease, invariably tilts the treatment decisions in the favour of palliation. Patients with head and neck squamous cell carcinoma also have issues pertaining to nutrition. From early in the course of the disease, the growth obstructing the aero-digestive tract or pain associated with the lesion compromises the swallowing ability. Thus with a chronic nutritional deficiency, these patients usually report with a compromised performance status. Socio-economic issues have also been a major reason for delaying or defaulting protracted courses of radiation treatment among our patients.

9. Role of Radiation in Palliation:

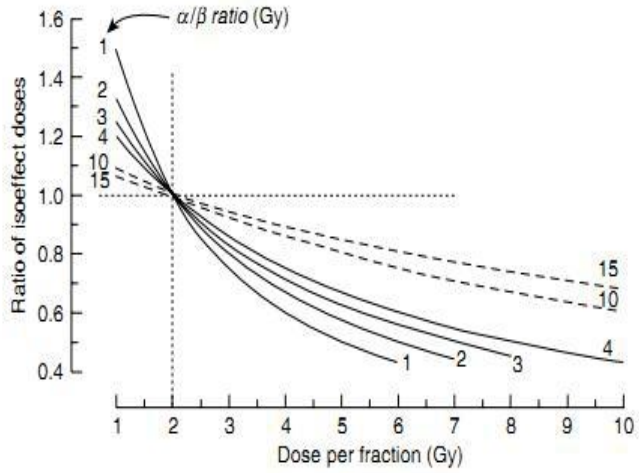
Due to the involvement of the upper aero-digestive tract, the patients often present with severe symptoms and there are no evidence based guidelines for standard practice of palliative care in advanced head and neck cancer. [45, 46] With advanced lesions and poor performance status, surgery is generally not feasible, considering sizeable amount of disease would still be left behind. Chemotherapy has shown little efficacy in palliation of bulky head and neck cancer lesions. Despite sufficient evidence on the benefits of palliative hypofractionated radiotherapy in patients with advanced solid tumours, there is scarcity of such data in advanced HNSCC. Poor patient compliance to treatment, limited enrolment cause difficulties in outcome assessment. Limitations with respect to personnel, radiation delivery equipment in developing countries makes timely delivery of palliation difficult. The role of radiotherapy in the palliation of advanced HNSCC is not clear. [47] A short course of high dose radiation can downsize the bulk of the tumour within short span of time, resulting in good symptom relief with minimal residual toxicity. However, there are still no appropriate tools or batteries to assess for symptom relief or effectiveness of palliative radiotherapy in HNSCC.

10.Study Rationale:

The paucity of data regarding the optimal use of hypofractionated radiotherapy in head and neck cancer for a population where 60-70% cases usually present in very advanced stages, has been the idea behind this study protocol. Hypofractionation implies use of larger dose per fraction with lesser number of fractions so as to deliver the equivalent biological effective dose (BED) in a shorter duration of time. Figure 1.10.1 indicates that for an increase in dose per fraction (d_f) over the reference value of 2 Gy, for an isoeffect, the total dose should be reduced as indicated by the curve. Due to a low $^{\alpha}/_{\beta}$ ratio, curves for late reactions are steeper than those for early reactions and for tumours, which have a high $^{\alpha}/_{\beta}$ ratio. Hence, if d_f is increased to 4 Gy per fraction and considering the $^{\alpha}/_{\beta}$ ratio for late reacting tissues to be 3 Gy, then the total dose must be reduced to 0.75 of its reference value i.e. a 25% reduction. For the tumour tissue, the $^{\alpha}/_{\beta}$ being 10 Gy, with d_f of 4 Gy, the isoeffective total dose of the tumouricidal dose (70 Gy) would work out to be about 58 Gy. A reduction by 25% will thus under dose the tumour and compromise local control. Large dose per fractions are

radio-biologically unfair as the late reactions are enhanced considering the lower $^{\alpha}/_{\beta}$ ratio for these tissues. However, the radiobiological principles are not minded as the aim of this study is only palliation of symptoms and not local control, and also, as the expected survival is far lesser than the time required for onset of late symptoms. Hypofractionated schedules have the advantage of being more convenient for the patient, their care takers and also for health care providers by sparing essential resources.

Figure 1: Isoeffect relationship



Compared with a reference treatment using 2 Gy per fraction, the diagram shows how the total dose must be changed in order to maintain a constant level of effect when dose per fraction is modified. Full lines are for low α/β ratios (as in late-responding normal tissues), and broken lines are for early-responding normal tissues or for most tumours.

The LQ model (linear – quadratic) helps in calculating isoeffect relationships for radiotherapy based on common basic assumptions, thus it makes the computation of different dose fractionation schedules easy. The effectiveness of different schedules of different total doses and doses per fraction can be easily compared by converting each schedule into an equivalent dose of 2 Gy fractions which would give the same biological effect. The equation for the above use is given as:

$$EQD_2 = D \frac{d + (\alpha/\beta)}{2 + (\alpha/\beta)}$$

Here, EQD2 is the dose in 2 Gy fractions that is biologically effective to a total dose D delivered using the dose per fraction of d Gy. Since 2 Gy is a commonly used fractionation, it helps in communication among different radiation oncologist specialists and therapists regarding the efficacy of a given dose fractionation schedule.

11. Concept of overall treatment time (OTT):

Radio-biologically speaking, overall treatment time is one of the major factors which governs treatment response. Biological effects of

radiotherapy are known to be compromised with increase in the overall treatment time. Initial radical trials were formulated in split-courses so as to reduce acute normal tissue toxicity. However, with the observation that even the tumour control is compromised, this practice has been given up. Accelerated repopulation is known to occur in head and neck cancer with a lag phase. Continuous Hyper-fractionated Accelerated Radiotherapy (CHART) study in head and neck cancer has established that onset of accelerated repopulation begins at 22 days. [48]Various other studies have given the range to be around 21 – 30 days.

12.Rationale for Split Course:

The dose of 20 Gy given in 5 fractions of 4 Gy each, is a sizeable dose over a short period of 5 days with a BED value of 28 Gy_{10}. To allow for normal tissue recovery from the acute toxicities of this dose, a gap of 2 weeks is allowed. It has been shown that mucosal regeneration time in head and neck is 3 – 4 days [49]. Also, the assessment at the end of two weeks helps to decide upon the patients that are suitable for a high dose treatment for achieving the goal of apt and prolonged symptom relief. Thus, after the recovery, one more

dose of 20 Gy is delivered similarly in 5 fractions. In a European study, a gap of 3 weeks was given for a total course BED value of 78 Gy delivered in two split courses. For our study, the total radiation course BED value is calculated to be 56 Gy, delivering 28 Gy in each course. Delay until the onset of accelerated repopulation largely minimises the effect of the 2 week gap on tumour response in this particular treatment schedule which has an OTT of 28 days. Thus, the treatment is planned to complete just beyond the accelerated repopulation is set in. The Equivalent dose in 2 Gy for this regimen is 46.7 Gy using $^{\alpha}/_{\beta}$ of 10 Gy for acutely reacting tissue and tumour tissue. Thus, if the dose recovery per day as a result of tumour repopulation is considered to be 0.7, the dose recovered by the tumour tissue with the two week gap can be calculated to be 4.2 Gy. Though it is not warranted, in a palliative setting where symptom relief and not abolishment of all tumour clonogen is the primary goal, accelerated repopulation is less of a concern.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Use of radiation in medicine dates back to late 19th century after the discovery of radioactivity and effects of x-rays. Since then, the field of radiotherapy has grown by leaps and bounds from initial superficial and deep xray, orthovoltage units to megavoltage treatment using Co-60 unit or the modern day Linear Accelerators (LINAC). There has also been development in delivery techniques with the advent of conformality and intensity modulation of the treatment beams under computer guidance. The various external beam radiation (EBRT) technologies are described below:

a. Co-60 EBRT Unit:

The inception of Co-60 treatment units for clinical use was in early 1950s. The advantages of this unit are cost effectiveness, easy availability, short treatment times, low maintenance, and personnel-efficiency. The major disadvantage of cobalt unit is the radio-active treatment source exposing the personnel to radiation risk. Usual treatment is 2 Dimensional where the minimum standard of care today is 3 Dimensional therapy. Other disadvantages include regular change of source due to decay, prolonged treatment times towards the end of

source, frequent re-calibration for output assessment. Only photon beam therapy is possible, electrons and neutrons though produced secondarily, are not of any clinical significance.

b. Linear Accelerator (LINAC):

Linear accelerators came into use for oncologic therapy in the early 1970s. The major advantage of this unit is no radioactive source thus eliminating the issues of personnel exposure, source decay, output calibration and source change. A variety of beams and energies such as photons (4, 6, 15 MV) and electrons (6-18 MeV) can be produced and chosen for treatment as desired. Electron beams are of advantage for treating superficial tumours. Higher energy beams have the unique "skin-sparing" effect. It also allows for 3-D treatment, and use of intensity modulated RT after mounting multi-leaf collimators. The disadvantages of LINAC units are primarily high costs, in a resource strained country like ours followed by high demand of trained personnel, treatment time, patient load, high maintenance costs, and rigid quality assurance requirements.

c. 3D Conformal Therapy:

With advances in physics, deeper concepts of three dimensional picture came into picture. It was understood that 2D fields were responsible for irradiating excessively large volumes of normal tissue which lead to toxicity and morbidity. Thus, with the help of Styrofoam blocks, fields conforming to the tumour tissue could be planned with minimal margin of surrounding normal tissue. However, preparation of Styrofoam blocks made the procedure tedious and lesser centres practice manual conformal technique now.

d. Intensity Modulated Radiation Therapy:

Further advances were with the development of multi-leaf collimators, which are basically lead blocks which can move in sync or separately so as to design an irregularly shaped field. Also, the dose to various parts of the tumour can be pre-planned with high doses in the bulk and lesser dose for the microscopic disease margin. The dose prescription then follows a complex logarithm so as to plan the MLC design, location and duration. This is known as “inverse planning”. This technique also helps in giving a boost dose to the gross tumour along

with the daily fraction which is known as “simultaneous integrated boost”.

e. Image Guided Radiation Therapy:

In the recent years, concern has been expressed over tumour motion during radiation delivery (intra-fraction) and between the consequent radiation fractions (inter-fraction). Techniques such as gated radiotherapy, on-table imaging, and 4D imaging have evolved to compensate for tumour motion. Gated radiotherapy with-holds the beam delivery when the tumour is detected to move out of the field of irradiation until it returns back. The tumour motion is detected by the closed system of metal clips placed in the tumour, infrared receivers placed over patient’s skin near the tumour and ceiling mounted infrared emitters. On-table imaging verifies the tumour location with the help of megavoltage x-rays, just before the delivery of every radiation fraction. 4D imaging incorporates the 4^{th} dimension of time while acquiring CT imaging for planning. The computer detects tumour motion during the scan and arranges the images according to different phases of respiration temporally. Thus, the entire range of tumour motion is acquired in a 4D scan which can be either be used for expanding the CTV plan

accordingly or for gated radiotherapy. Image guided radiotherapy can be practiced using a simple Co-60 unit as well with on board imaging facilities.

f. Stereotactic Radiation:

Use of computer guided treatment planning and delivery is of utmost benefit in Stereotactic Radiotherapy techniques (SRS/ SBRT) where the system delivery accuracy lies within millimetres, which is required considering these techniques are used to deliver large doses to small volumes that are placed more often in eloquent areas. Image guidance is of utmost importance for practicing Stereotactic radiation. Stereotactic radiation can be delivered as a single high dose of radiation or as a fractionated treatment. When given in high doses, immediate tumour kill is achieved thus, being regarded as stereotactic radio**surgery** as it is likened to a surgical tumour removal. SRS/SRT can be practiced using a LINAC, Gammaknife or Cyberknife™ machines.

g. Heavy Particle Radiation:

In the recent years, there has been great interest regarding the use of heavy particle beams like protons, carbon ions and neutrons. These

particles characteristically exhibit Bragg peak effect i.e. rapid dose build up at a depth followed by a sharp fall off. [50]Thus, the heavy particles are of particular interest in HNSCC, where the tumours are often surrounded by at-risk dose-limiting structures namely the parotid gland, pharyngeal constrictors. [51, 52]Recent studies have shown excellent parotid sparing and feasibility of high dose delivery with use of intensity modulated photon beams. However, because of huge costs involved in maintenance, personnel training and treatment with these machines, worldwide, very few centres practice this technique.

Patient Treatment Selection in Advanced Head and Neck Carcinomas:

There have been no definitive guidelines, prognostic or selection factors that guide treatment protocol selection in these cases. Radical loco-regional therapy is recommended to harness the possibilities of a cure. There have been conflicts often in minds of decision makers to identify patients suited for palliation alone as against those taken for curative therapy. The treating physician should consider the following aspects in absence of any consensus guidelines for deciding patients suitable for palliative treatment:

a. Inoperability

b. Poor performance status

c. Co-morbidities

d. Short life expectancy

e. Advanced spread of the tumour where cure is unrealistic

f. Metastatic disease

g. Socio-economic factors

h. Symptom relief with minimal therapy is possible

Chemoradiation in Advanced Head and Neck Carcinomas:

Standard of care for advanced unresectable HNSCC in patients with a favourable performance status is chemoradiation. Several randomized controlled trial's data have shown that chemoradiation improves local control and provides a survival benefit compared to radiation alone. The rationale for combining chemotherapy with radiation are:

a. **Radio-sensitisation:** The chemotherapeutic drug gets selectively taken up and concentrated in the tumour tissue and making them sensitive towards radiation induced cell kill. Radio-sensitizers do not have any inherent cytotoxic action.

b. **Spatial co-operation:** Radiotherapy acts loco-regionally while chemotherapy acts systemically to control the micro metastases. Radiation and chemotherapy do not act in synergy.

c. **Cytokinetic co-operation:** Administration of the chemotherapeutic drug organizes the cells in particular phase of cell cycle such that the effect of radiation delivered subsequently, is enhanced.

d. **Hypoxia prevention:** Cytotoxic drugs like paclitaxel improve tumour perfusion and oxygenation by direct action on tumour cells and reducing the tumour bulk.

e. **Normal tissue protection:** Drugs like amifostine show selective uptake into the normal tissues and prevent platinum-DNA adducts along with free radical scavenging, thus reducing normal tissue toxicity.

f. **Prevent tumour repopulation:** Accelerated tumour repopulation is known to set in after a potent cytotoxic stimulus. For HNSCC, tumour repopulation has been shown to set in as early as 10-14 days after initiation of the radiotherapy. Thus, along with radiation, cytotoxic

chemotherapy provides a supra additive effect to counteract the tumour re-population.

Chemotherapy in relation to radiation can be delivered in the following sequences/ techniques:

1. **Sequential Chemoradiation:**

The early trials combining chemotherapy and radiation utilized the technique of sequencing chemotherapy first followed by definitive radiation, so as to control for the toxicities. The Department of Veterans Affairs Laryngeal Cancer Study Group compared 'sequential therapy using three cycles of Cisplatin and 5-Flurouracil' with 'total laryngectomy followed by radiation' for stage 3 or 4 laryngeal cancers. They observed that larynx was preserved in 64% cases at the end of 2 years. It was concluded that sequential chemotherapy increased the effectiveness of definitive radiation. However, the study was not designed to compare sequential chemoradiation with radiation alone. An update to the trial results later showed that complete response rates were 42% at the end of cytotoxic treatment. Thus, it proved that organ preservation was a possibility without affecting the survival of these patients.[53]

2. Concurrent Chemoradiation:

With advances in science and greater understanding of the tumour biology and of responses to chemoradiation, agents like Cisplatin and its combinations have been tried in various trials. The exact benefit and advantage of chemotherapy along with radiation was a grey area until Pignon et al came up with the updated data on meta-analysis of chemotherapy in head and neck cancers (MACH-NC). [40]The data showed an absolute benefit of chemotherapy to be 6.5% at five years. No significant difference on survival was observed with addition of chemotherapy. Multi-agent chemotherapy did not show any benefit in the concurrent setting compared to single agent regimens. Among the various drugs tried as single agent viz. Taxols, 5-Fu, Capecitabine, none showed superiority to Cisplatin. Only one trial which used cumulative doses of 140 mg/m^2 of Cisplatin showed negative results, thus indicating that total dose of Cisplatin to achieve the proven benefit is important.

3. Induction Chemotherapy:

Recently, Pointreau Y et al in a randomized trial of laryngeal and hypopharyngeal SCC showed that overall response rate and 3-

year actuarial larynx preservation rate was higher with TPF (Docetaxel with Cisplatin and 5-FU) compared to PF alone, however, at the cost of increased acute toxicity. [54, 55, 56]The two landmark trials, DeCIDE[57] and PARADIGM[58]have compared the effectiveness of 'induction chemotherapy followed by concurrent chemoradiation' with 'concurrent chemoradiation alone'. DeCIDE trial was to determine the survival benefit of treating with induction chemotherapy prior to concurrent chemoradiation. The induction chemotherapy regimen used was (TPF) Docetaxel, Cisplatin, 5-Flurouracil while during the concurrent phase, combination of Docetaxel, 5-FU, Hydroxyurea was used along with hyper fractionated radiotherapy. Though the results showed a reduction in distal failure, it failed to show any improvement in OS. The PARADIGM trial as well did not show any significant survival advantage with incorporation of the induction chemotherapy to concurrent chemoradiation.

Thus, all the available literature supports the use of single agent Cisplatin concurrently with radiation. RTOG-0129 and Intergroup studies have demonstrated the minimum threshold cumulative dose of Cisplatin to be 200mg/m^2 for obtaining benefit.

Palliative Chemotherapy in Unresectable Head and Neck Carcinomas:

Surgery is the recommended option for HNSCC, however, when the disease is unresectable the options are concurrent chemo radiotherapy if PS is good or else palliative treatment in the form of single agent radiotherapy or chemotherapy. Chemotherapy alone has less of a role in HNSCC and its mainstay is in the setting of metastatic disease/ recurrence that is unresectable or previously irradiated. Single agents and combination therapies have been tried in the scenario of recurrent/ metastatic disease. Despite all available chemotherapy regimens, median overall survival has remained less than 1 year in these patients.

There was an early study designed to find the advantage of combination of Cisplatin and 5-Fluorouracil versus their use as single agents. An improvement in overall response rate was observed with the combination regimen compared to use of either Cisplatin or 5-Fluorouracil alone, though at the expense of increased toxicity. Patients with better PS and poorly differentiated tumours had a trend

towards better survival, however, they did not observe any significant difference among the two arms with respect to median survival. [59]

Later, with introduction of newer taxanes, EORTC investigated the role of single agent Docetaxel for advanced HNSCC. They observed a response rate of 32% (95% CI 17-47%) but along with a 61% incidence of short-lasting grade 3-4 neutropenia. They however concluded that, Docetaxel is an active drug and that the toxicities were manageable with supportive therapy. [60]

With notable activity of vinca alkaloids in various solid tumours, efficacy of Vinorelbine was evaluated in a phase II study of recurrent or metastatic lesions. Overall response rates of 14% were observed, with median duration of response being 19 weeks. Grade 3-4 toxicities were observed in 53% of the patients while treatment related deaths were reported in two patients.[61]

Further, an inter group trial of ECOG was undertaken for comparing the combination regimens viz. Cisplatin/ 5-FU and Cisplatin/Paclitaxel. No significant differences in survival or response

rates were observed. Toxicity profile of both the treatments arm were also similar. Thus, this trial was negative and both the arms were equally effective in matched individuals. [62]

In beginning of the 21st century, Cetuximab, a monoclonal antibody against epidermal growth factor receptor (EGFR) was developed. Thus, Herbst RS, et al studied the efficacy of combining cetuximab with cisplatin with **"EXTREME"** trial. All patients were initially randomized to receive 2 cycles of either Cisplatin/ Paclitaxel or Cisplatin/ 5-FU. Those with stable or progressive disease were switched to combination of Cetuximab (weekly 250 mg/ m^2after loading dose of 400 mg/ m^2) along with Cisplatin (100mg/m^2 q21days). Objective response rates were observed in 44% of cases. Median duration of response and median overall survival were higher for patients that showed initial stable disease (7.4 months and 11.7 months respectively) vs progressive disease (4.2 months and 6.1 months respectively). Authors concluded that Cetuximab and Cisplatin combination is active and Cetuximab did not exaggerate the toxicity of the latter. [63]

ECOG study group, formulated a phase III trial to assess if the addition of Cetuximab to Cisplatin improved the progression free survival (PFS). All patients were planned to receive Cisplatin every 4 weeks along with either weekly Cetuximab (Arm A) or placebo (Arm B). Median PFS in trial arm was 4.2 months vs 2.7 months in the placebo arm. Median OS was 9.2 months (Arm A) vs 8 months. Objective response rates were 26% (Arm A) vs 10%. Thus, the conclusion drawn was that, addition of Cetuximab significantly improves response rate however, PFS and OS were not significantly improved. [64]

The Southwest Oncology Group (SWOG) evaluated the combination of Docetaxel/ Carboplatin in advanced HNSCC. Response probability was 25% with 95% CI: 15-38%. Median PFS and OS were 3.8 months and 7.4 months. Considering that 61% of the patients experienced grade 3 or worse neutropenia, it was suggested that the regimen is active for patients with good performance status. [65]

The largest evidence towards combination of cetuximab with PF comes from the study by Vermorken JB et al, where they randomized a total of 442 patients into PF alone or PF + cetuximab. The study documented a significant prolongation of median overall survival from 7.4 months to 10.1 months in the combined therapy arm. It also significantly prolonged the median PFS time from 3.3 to 5.6 months and the response rates increased from 20 to 36% ($p<0.001$). Incidence of grade 3 toxicity was low and overall toxicity profile appeared favourable. Thus, this trial provided the necessary evidence base for NCCN to make this combination, a category 1 recommendation for first-line treatment of recurrent/ metastatic HNSCC. [66]

After the success of cetuximab, smaller tyrosine kinase inhibitors such as Gefitinib were tried by Stewart JS, et al. They compared the survival of patients treated with 2 doses of Gefitinib with the then standard of methotrexate. This trial was negative as neither 250 mg nor 500 mg of Gefitinib per day improved survival when compared to methotrexate. The three arms were similar with

respect to median overall survival, objective response rates or QoL improvement rates.[67]

Other regimens used were weekly Paclitaxel and monotherapy with Capecitabine. Weekly Paclitaxel was found to be as active as any other single agents. The toxicity profile was acceptable. [68] Use of Capecitabine also showed similar results. [69]

Thus, to summarise, with all the available data from various clinical trials, there is enough evidence on hand to prove that various drugs used in monotherapy provide a 10-25% tumour response with a median survival of 6-8months. Combination therapies may increase the response rates up to 45-50% but without improving the survival. Only the triplet of PF plus Cetuximab has shown a survival advantage of up to 10.4 months and is now the standard of care. [70] Recently, the phase II trial GORTEC 2008-03 on an interim analysis suggested that Docetaxel, cisplatin along with cetuximab is effective with a manageable toxicity profile and might substitute the present standard of care.[71]

Palliative Radiation in Advanced Head and Neck Carcinomas:

Palliative radiotherapy aims at improving the quality of life with control of symptoms, it may or may not produce prolongation of survival. Existing literature is not substantial at present, to formulate guidelines regarding optimal palliative regimen with respect to time, dose and fractionation. The available evidence comes from various retrospective or case-control studies, single arm prospective trials and few small randomised controlled trials which have shown an improvement in outcome. [46, 47]

Institutional policies vary in practices of palliative radiation with respect to fractionation, from conventionally fractionated radical doses of 60-70 Gy to short courses of hypofractionated radiotherapy. The idea of Hypofractionation is to strike a balance between quick and effective symptom relief against treatment toxicity. However, it is of concern whether protracted courses of radiotherapy with doses equivalent to curative schedules and their resultant increased toxicity actually improve outcome.

A large study on natural history of untreated advanced HNSCC followed 808 patients from 1953-1990, until death and offered best supportive care in view of advanced tumour stage or poor performance status. Median overall survival was observed to be 3.82 months (range: 1 day to 53.8 months). PS was the only significant predictor of outcome and survival. Those with better PS, favourable tumour location and extent were seen to survive for 4 or more years. The inference drawn was that palliative radiation neither improved survival or QoL of these patients. [72]

Similarly, Carvalho et al [73] analysed data from patients of advanced HNSCC, who were treated and those who were not treated until demise. Though their initial report was negative, later significant differences were observed with respect to survival in the two arms. The type of treatment or the tumour response to therapy did not influence the survival.

Literature speaks of only a single randomised controlled, prospective trial testing the efficacy of short course hypofractionated radiotherapy of very advanced unresectable HNSCC dates back to late

20th century conducted by Weissberg JB, et al. A small population of 64 patients was randomised to receive 60-70 Gy in conventional fractionation (2 Gy/ fraction in 30-35 fractions over 6-7 weeks) or short-course hypofractionated radiotherapy of 40-48 Gy (4 Gy/fraction in 10-12 fractions over 2-3 weeks). The two arms were comparable with respect to tumour response, toxicity, symptom relief and overall survival. [47]

Another study conducted by Burns, et al. studied the records of 76 patients treated with radiation of either curative or palliative intent. Patients treated with curative intent had mean OS of 19.4 months compared to 8.4 months in palliative arm. 2 year DFS was observed to be 29% in curative arm. Advanced stage in itself was a poor prognostic factor with mean survival of patients observed to drop down to 7.5 months with T4 tumour. Palliation of symptoms was deemed to be reasonable in 25% patients. However, they concluded that palliative radiotherapy was no better than best supportive care and that there was little benefit associated with treatment. [74]

A retrospective analysis of 40 patients with advanced disease who were treated with either 30 Gy/ 10 fractions/ 2 weeks or 20 Gy/ 2 fractions weekly, showed a good 1 year response rate of 65% and 48% respectively and symptom relief rate of 57% and 38% respectively. The absolute survival as well as the cause-specific survival rates were 25% at 1 year. Successful palliation was achieved in greater than 50% of the patients treated with palliative intent. [75]

A series of 331 senior adults (> 70 years) was studied by Lusinchi, et al. Out of the total, 54 patients received 30 Gy in 15 fractions over 3 weeks with palliative intent. Those with appreciable response (50%) were treated further radiotherapy to curative doses. The results published show that 33% patients could not complete the initial planned radiation dose of 30Gy due to low tolerance to radiation, poor PS or progression. Overall, the immediate and long-term toxicities of radiation were favourable. Local control rate was 19% at 3 years. OS at end of 2 and 5-years were 16% and 5% respectively. Due to retrospective nature of the study, symptom relief and QoL benefits could not be assessed. [76]

Similarly, out of the 54 patients in a series of 160 patients treated with palliative radiotherapy, failure to complete planned course of radiation was seen in 33% due to disease progression or poor PS. At the end of two years follow up, two survivors were noted.[77]

With deeper understanding of radiobiological principles, a protocol was formed for cyclical accelerated split-course radiotherapy. Treatment delivered was 23.4 Gy/ 9 days, divided in 13 fractions of 1.8 Gy, twice daily from days 3 to 11, and this was repeated for 3 cycles on day 22 and day 44, to deliver total tumour dose of 70.2 Gy/ 51 days. The overall toxicities of the treatment were found to be acceptable. Excellent symptom palliation was achieved when compared to historical controls treated with palliative radiotherapy. With the mean follow up period of 21 months, out of the 32 patients treated, 28 achieved a complete response. Two year local control rate was 81% while the actuarial one and two year survival rates were 88% and 58% respectively.[78]

A phase I/II study[79] was performed using 3.7 Gy per fraction, twice daily over 2 consecutive days for a total of 14.8 Gy in 4

fractions. The schedule was repeated every 3-4 weeks to deliver a total dose of 44.4 Gy over 9-10 weeks. Of all the 37 treated patients, 84.6% achieved reasonable palliation with minimal acute toxicity. No patients were observed to have any long-term complications from the treatment. The mean survival was reported as 4.5 months. Complete response was achieved in 11 patients while about 50% of them had a partial response.

A study conducted by Minatel et al, investigated the role of a higher dose palliative regimen with concurrent low dose Bleomycin in unresectable HNSCC. Fifty eight patients were treated in a split course fashion to a total dose of 50 Gy delivered in 20 fractions. First 25 Gy were delivered along with concurrent Bleomycin (60 mg/ 6 cycles) followed by a 2 week gap before the second course of further 25 Gy. Authors reported a local control rate of 69%. Response was observed for a median of 7 months. Appropriate palliation was achieved in 81%. However, they also reported a grade 3 toxicity in 46.5% of the treated cases which was manageable.[80]

A recent retrospective study conducted by Stevens CM et al, examined the outcomes and prognostic factors for patients treated with radiation of palliative intent. Median radiation dose delivered in the analysable patients was 50 Gy (range 2-70 Gy) in a median fraction of 20 and median total treatment time being 29 days. Median survival time was found to be 5.2 months. They found on a multivariate analysis that, for patients considered unsuitable for curative radiation regimens, radiation dose was an independent predictor of overall survival as well as the treatment response. [81]

In "**Hypo Trial**" [82] conducted in Queensland by Porceddu SV et al, patients received 30 Gy in 5 fractions, 2 fractions per week which were atleast 3 days apart. In suitable patients, this was followed by an additional boost dose of 6 Gy for small volume lesion. Of the patients treated, 88% received the additional boost dose. Overall objective response was seen in 80%. An overall improvement in QoL was seen in 62% while 67% had improvement in pain scores. Median progression free and overall survival were 3.9 months and 6.1 months respectively. They concluded that the regimen provided effective palliation with excellent compliance and good symptom control.

The experience of Rotterdam Cancer Institute with the **"Christie Scheme"** was published in Acta Oncologica recently. Patients unsuitable for curative treatment were treated with hypofractionated radiotherapy of 16 fractions of 3.125 Gy each. An overall response rate of 73% was noted while 21% had progression during or immediately after completing the scheduled course of radiation. At one year, the actuarial DFS and OS were 32% and 40% respectively which declined to 14% and 17% by the end of 3 years. Median survival was reported as 17 months with this schedule. Grade 3 or greater skin and mucosal toxicity was observed in 45% and 65% patients respectively. Pain and performance status improvement was seen in 77% and 47% respectively. It was concluded that Christie scheme provided excellent palliation and symptom control with acceptable toxicity.[83]

At PGI Chandigarh, 25 patients of unresectable head and neck cancer were treated with short course palliative radiation consisting of 30 Gy delivered in 10 fractions over 2 weeks. An eleven-point numerical scale was used to assess baseline symptoms such as pain, dysphagia, cough, insomnia and dyspnoea. Symptom relief of greater

than 50% was observed at one month post-treatment among all patients with pain and over 90% of patients with dysphagia, insomnia and dyspnoea. Response was seen for a median duration of 3 months. None were reported to have grade 3 or greater toxicity.[84]

An All India Institute of Medical Sciences **(AIIMS) study** treated 505 patients with a short course radiation of 20 Gy, given in 5 fractions of 4 Gy each over a week. Two or more symptoms were present in 71% of the patients. At the first month follow up, 37% were seen to achieve a partial response to the treatment and also maintained a good performance status that made them amenable for further radiation to attempt cure. A symptom relief of more than 50% was deemed good and such a relief was noted in 57% patients with pain and hoarseness, 53% for dysphagia, 59% for cough and 76% for respiratory distress. Maximum reported toxicity was grade 1 to 2 mucositis and dermatitis. Median survival in treated patients was noted to be a little over 6 months. Those who received further radiation of curative attempt, had an improved overall survival of over a year. Overall, 37% patients achieved a partial response. [43]

Further, the more popular regimen, the **QUAD-SHOT**, [85]consisted of 14 Gy in 4 fractions, twice daily at least 6 hours apart for 2 consecutive days and the entire cycle repeated at 4 weekly intervals for a total of three courses if no interim tumour progression was noted. The study was designed such that each cycle of radiation delivered the dose that was sub-optimal to that required for producing mucositis. At the same time, the maximum cumulative radiation dose was fixed considering the late effects of radiation. All patients had at least one cycle of radiation while 53% could complete all 3 cycles. Median OS was observed to be 5.7 months while the median PFS was 3.1 months. None had grade 3 or worse toxicity and the tolerance was good with 44% reporting an improved overall QoL. This trial had a unique feature of patient rated judgement regarding the treatment worthiness. At the end of first, second and third cycle, 43%, 58% and 63% of patients respectively, found the treatment worthwhile.

Theoretically, a higher total dose is required for maintaining reasonable palliation and controlling the tumour growth. Though various studies describe various schedules and fractionation schemes, overall, the literature supports the use of short-course, split-course or

the cyclical regimens compared to single large fraction treatment for palliation of very advanced head and neck cancer.

Split-course Hypofractionated Radiation:

Split-course hypofractionated regimen is an attractive option for palliation of advanced unresectable head and neck cancer cases considering the following advantages:

a. **Effective** regimen in various studies in literature
b. Good **symptom palliation**
c. Allows for normal tissue recovery in the two week gap and **minimising toxicity**
d. Works with **minimal** load on **resources** or personnel
e. **Short course** treatment making it acceptable for the patient, weighing the socio-economic factors
f. Small hospital stay **minimising health care costs**

Kancherla KN et al, [86]reviewed their institutional protocol at St.James Institute of Oncology, Leeds for palliation of advanced, unresectable head and neck cancer cases. Patient selection was done after discussion in a multi-disciplinary tumour board. Stage grouping

alone was not adequate and other factors including tumour extent, performance status, co-morbidities and socio-economic factors were taken into consideration before offering the option of palliative radiation. Patients who had received prior palliative chemotherapy were excluded. The protocol consisted of an initial course of 20 Gy in five fractions of 4 Gy each over one week followed by a two week gap. Patients were assessed for toxicity and responses at the end of the two week gap and those deemed fit were treated with a second course of similar 20 Gy radiation over a week. Radiation was delivered with parallel opposed fields, encompassing the gross tumour volume (primary tumour and nodal disease) along with a 1 to 2 cm margin, where required. Uninvolved nodes were not encompassed prophylactically. Maximum effort was taken to spare the uninvolved normal tissues. Where bulky disease infiltrated the skin, treatment was carried out with a surface bolus. Spinal cord tolerance was respected and fields modified after the dose of 37.5 Gy for late effects was received by the cord. Patients were assessed during the treatment and 4-6 weeks after its completion. During the assessment at the end of 2 week gap, those with major toxicities or disease progression were offered best supportive care. Symptomatic and tumour responses were

recorded on every assessment. Total of 44 patients were treated under this study out of which 11 received only the first course of 20 Gy. Further treatment was deferred in these patients due to treatment induced toxicity, disease progression or socio-economic factors. Symptoms at presentation were dysphagia (76%), pain (70%), breathlessness (24%) and hoarseness (24%). Two or more symptoms at presentation were seen in 73% cases. Reasons for taking these patients under palliative treatment were co-morbidities (54%), advanced age (39%) and poor PS at presentation (36%). Toxicity profile of the treatment was acceptable with only 18% experiencing some form of grade 3 toxicity. A major symptom improvement was noted in 52% of the cases, while 15% had no change and 6% had deterioration of symptoms. At the first follow up, 39% were shown to achieve a complete response while 33% had a partial response to the two courses of high dose radiation. Degree of response achieved correlated well with the symptom relief achieved. Median overall survival of the study population was noted to be 9 months (range: 3 - 43 months). At the last follow up, 24% patients were alive while 70% had expired as a result of disease progression, recurrence or metastasis. At 1 and 2 years, progression free survival rates were

observed to be 42 and 35% respectively. On further analysis, higher T stage was associated with poorer survival. Complete response to radiation was associated with significantly higher PFS and OS. However, with the aim of this study being palliation and symptom relief, the focus is less on a formal tumour response. The authors concluded saying that split-course hypofractionated radiotherapy was a feasible option for palliation and it offered a good symptom relief.

Thus, with this study, we are investigating the activity and feasibility of split-course hypofractionated radiotherapy among our population which largely consists of advanced, unresectable head and neck squamous cell carcinoma.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

Primary Objective:

To assess the symptom relief after a split course of palliative hypofractionated radiotherapy in patients with advanced head and neck squamous cell carcinoma.

Secondary Objectives:

a. To assess the Quality of Life (QoL) of these patients
b. To assess the treatment related toxicity
c. To assess the immediate loco-regional response

MATERIALS AND METHODS

MATERIALS AND METHODS

The study design was a single arm, prospective study determining the activity of split course hypofractionated radiotherapy for palliation of advanced head and neck squamous cell carcinoma.

The study protocol was formed and submitted to Institutional Ethics Committee. The patients were accrued into the study only after obtaining the necessary approval. Signed informed consent was obtained from all the patients who fitted the inclusion criteria and were willing for treatment under the prescribed study protocol. The study period was from January to August 2014.

1. INCLUSION CRITERIA:

- Biopsy proven squamous cell carcinoma of the head & neck (SCCHN)
- Primary tumour sites: oral cavity, oropharynx, hypopharynx, larynx
- Stage 3 or 4 disease without evidence of distant metastases
- No previous surgery/ chemotherapy or radiotherapy
- ECOG performance status >2
- Age < 70 years

- Medically manageable co-morbidities
- Signed informed consent prior to initiation of protocol specific procedures

2. EXCLUSION CRITERIA:

- Previously received treatment for any other malignancy
- Tumours of nasal cavity, paranasal sinuses, nasopharynx and salivary glands
- Non squamous histopathology
- Uncontrolled co-morbidities

3. PRE-TREATMENT WORK UP:

a. History and clinical examination: To note down the time to onset of illness and symptoms, see the extent of the tumour and regional nodes for accurate clinical staging.

b. Symptoms at presentation: Patient might be having one to many symptoms at the time of presentation, recording the severity of each symptom.

c. Biopsy from tumour: Squamous cell carcinoma constitute 90% of the head and neck cancer. Other uncommon histology can be adenocarcinoma, adeno-squamous, mucoepidermoid, lymphoepithelioma, lymphoma, etc. For this study, only squamous cell carcinoma is the inclusion criteria.

d. Performance status: Many studies have shown a correlation between performance status and survival outcomes in cases of advanced head and neck cancer given palliative treatment.

e. Height and weight: To calculate the body surface area for drug dose calculations.

f. Blood investigations: Complete blood count, renal and liver function tests before initiation of each radiation course.

g. CT scan Neck: From base of skull to Root of Neck– Plain and Contrast before start of treatment and 4-6 weeks after completion.

h. Chest X ray – PA view: With advanced nodal disease, risk of lung metastasis increases in head and neck cancer. Pharyngeal sub-sites with nodal disease of N2 or greater have about a 15% risk of lung secondaries.

i. Dental evaluation and prophylaxis: To minimise the risks of dental sequelae namely, caries, infections and osteoradionecrosis.

j. Diet plan: Specific high protein diet plans were formulated for patients undergoing high dose radiotherapy with the help of institutional dietician.

k. Feeding procedure as warranted: Those presenting with severe pre-treatment weight loss, dysphagia or airway obstruction.

l. Counselling to quit tobacco use: Every patient counselled personally for helping them to quit tobacco and related products. Continued smoking during treatment has shown poor outcomes.

TREATMENT PLANNING:

All patients were treated with parallel, opposed, lateral paired fields encompassing the gross disease and the draining lymph nodes. The treatment fields were open, non-wedged and without any beam attenuators, with dose prescribed to the midline depth of the two fields. Surface bolus was used were tumour or the nodal disease invaded the skin in the form of ulceration, fungation or necrosis.

RADIOTHERAPY SCHEDULE:

All patients after the initial staging and general work up and assessment were planned for radiotherapy. Radiotherapy was scheduled

in two courses, split by a two weeks gap for allowing normal tissue recovery.

Each radiotherapy course consisted of 20 Gy delivered in 5 fractions of 4 Gy each, one fraction daily. Radiation was delivered in a 2-D setup using Co-60 tele-therapy unit, in parallel opposed fields. Gross tumour and the nodal disease were encompassed in the fields. Prophylactic irradiation of uninvolved nodes was not carried out. Spinal cord tolerance was well respected with the posterior border of the field shifted anteriorly to avoid spinal irradiation beyond the EQD_2 of 40 Gy. Tight margins were given around the gross disease in an effort to minimise the toxicity to uninvolved normal tissues.

Effort was made to start the radiation on first day of the week so as to complete the fractions by the fifth day of the week. Patients were then given a two week gap from the fifth fraction to attenuate the normal tissue toxicity. Treatment was delivered using surface bolus in cases with skin infiltration or nodal ulceration. They were then re-assessed at the end of the two week period for symptom relief and toxicities out of the first course of treatment. Those with less than or

equal to grade 2 toxicities were further treated with another course of 20 Gy radiation in further 5 fractions. Those with greater than grade 2 toxicity were offered Best Supportive Care (BSC). Patients in whom the second course of radiation was delayed beyond the two week gap period due to worsening of performance status, were considered to have received only one course under the protocol.

The Biological Equivalent Dose (BED) of the entire course of therapy was 56 Gy_{10} with an Equivalent Dose in 2 Gy (EQD_2) of 46.7 Gy for the tumour and for late reacting tissues, BED was 93.3 Gy_3 with EQD_2 of 56 Gy, unminding the two week gap.

PATIENT CARE DURING TREATMENT:

a. Watchful assessment of toxicities; suspension of radiation when treatment toxicity exceeded grade 2.
b. Oral hygiene- mouthwash, regular oral rinsing, anti-fungal and antibiotics when clinically indicated.
c. Dietary management and nutritional care
d. Other basic symptomatic management with respect to cough, dyspnoea, insomnia etc.

ASSESSMENT:

Following assessments were done on pre-defined time intervals for all patients that were treated under this study protocol.

a) **Symptoms:** Symptoms were assessed before initiation of treatment, at the end of first course of radiotherapy, at the beginning and end of second course of radiotherapy and at the first month follow up. Symptoms were assessed and gauged using the symptom relief assessment scale at the end of treatment to assess the activity of the given treatment. The symptoms were recorded on a scale of 0 to 4 during each assessment. The change in symptom scores were calculated by the differences between the readings at different time points. An improvement in symptom was thus denoted by a negative score (-) at the time of evaluation, while worsening of symptom was scored with a positive sign (+) post-fixed to the number.

b) **Toxicities:** Toxicities to the treatment were assessed using RTOG Acute Morbidity Scoring Criteria and Common Toxicity Scoring Criteria Version 4.03. They were assessed before the initiation of

second course of radiotherapy and at the first month follow up after completion of radiotherapy course.

c) **Quality of Life (QoL):** Quality of life was assessed in all treated patients at the first month follow up after treatment completion using the patient rated questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC), quality of life Questionnaire – QLQ C30.It measures the Quality of Life on the basis Global Health Status (2 point), Functional Scale (15 point) and Symptom Scale (13 point). All symptoms scales were noted and scored however, symptoms specific to head and neck cancer were evaluated and analysed in detail. It was compared to the QoL scores assessed at the base line and the improvement in QoL was thus calculated.

Formulae for assessment:

Raw score: $RS = \frac{(I_1 + I_2 + I_3 + \ldots + I_n)}{n}$

Here, I_1, I_2, I_3,…In are the items included in a scale of assessment.

Functional Scales: $S = \left\{ 1 - \frac{(RS - 1)}{\text{range}} \right\} \times 100$

Symptom Scales/ items: $S = \left\{ \frac{(RS - 1)}{\text{range}} \right\} \times 100$

Global Health Status: $S = \left\{ \frac{(RS - 1)}{\text{range}} \right\} \times 100$

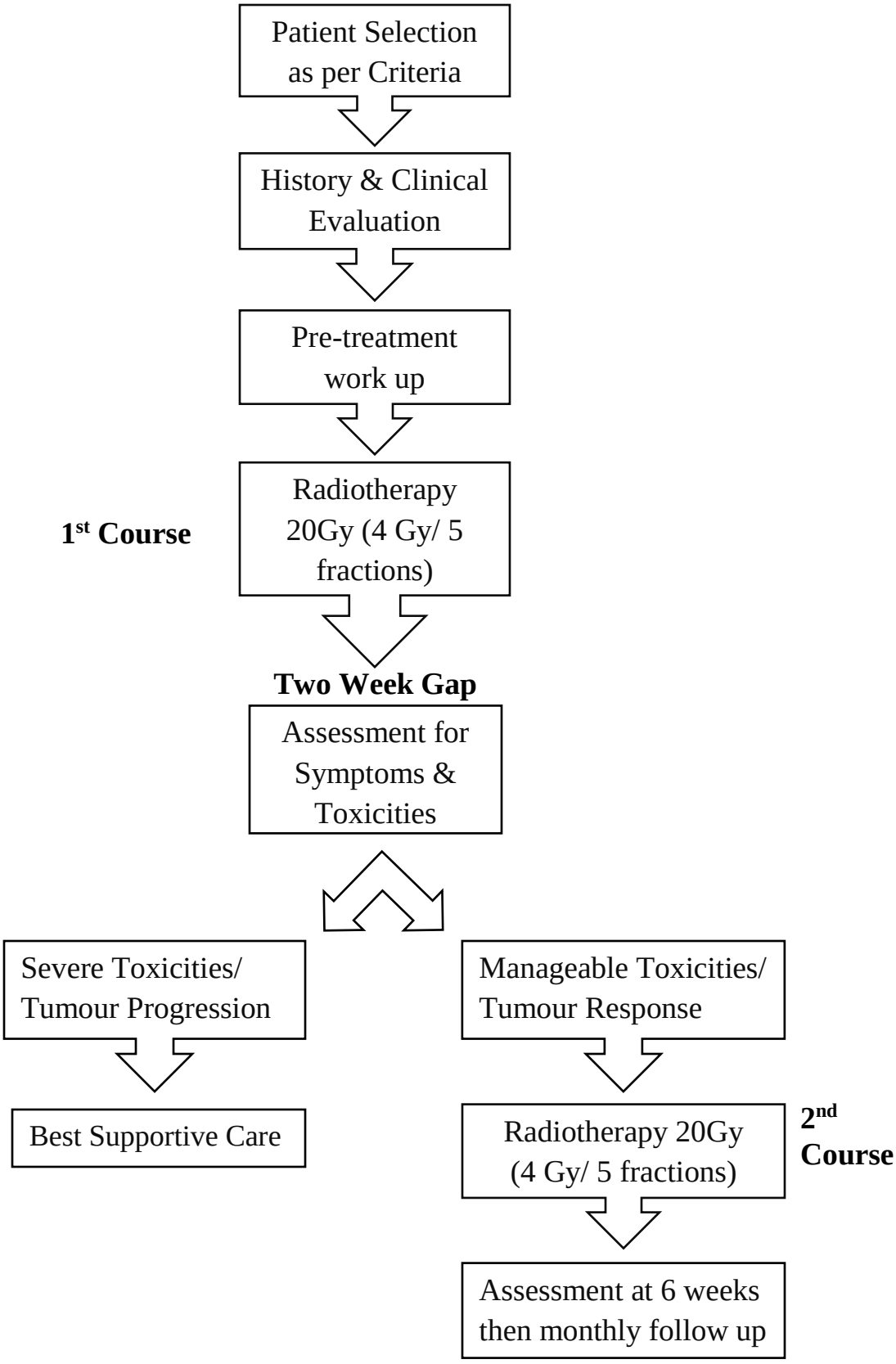
Range is the difference between the maximum and minimum possible value of raw score. The questionnaire is has been so designed that all items of any scale take the same range of values thus, range of raw score being the range of individual values.

d) Response Assessment: Treatment response was assessed at the first month follow up after the end of radiation treatment using the RECIST (Response Evaluation Criteria in Solid Tumours) version 1.1 for primary as well as nodal disease. Primary disease was assessed by clinical examination along with flexible endoscopy. Nodal disease was assessed by clinical examination. Overall response was assessed at the first month follow up with the help of imaging (Computed Tomography scans of the neck).

STATISTICAL ANALYSIS:

The statistical analysis and data computing was done using Microsoft® Excel™ 2013. Statistical 'significance' of the individual results could not be computed as the study was not powered enough.

STUDY DESIGN:



RESULTS AND ANALYSIS

RESULTS AND ANALYSIS:

Out of the 30 patients treated, all were available for analysis. Results were analysed on the 'Intention-to-treat' basis.

1. Age distribution (Table 1):

The age groups of 51-70 constituted the majority of the study population.

Age Groups	Count	Percentage Population
31-40	3	10.00
41-50	3	10.00
51-60	9	30.00
61-70	15	50.00

2. Sex Distribution (Table 2):

In our study group, population was largely male dominant, forming 73.3% of the total cases.

Sex	Count	Percentage Population
Male	22	73.33
Female	8	26.67

Figure 2: Age Distribution

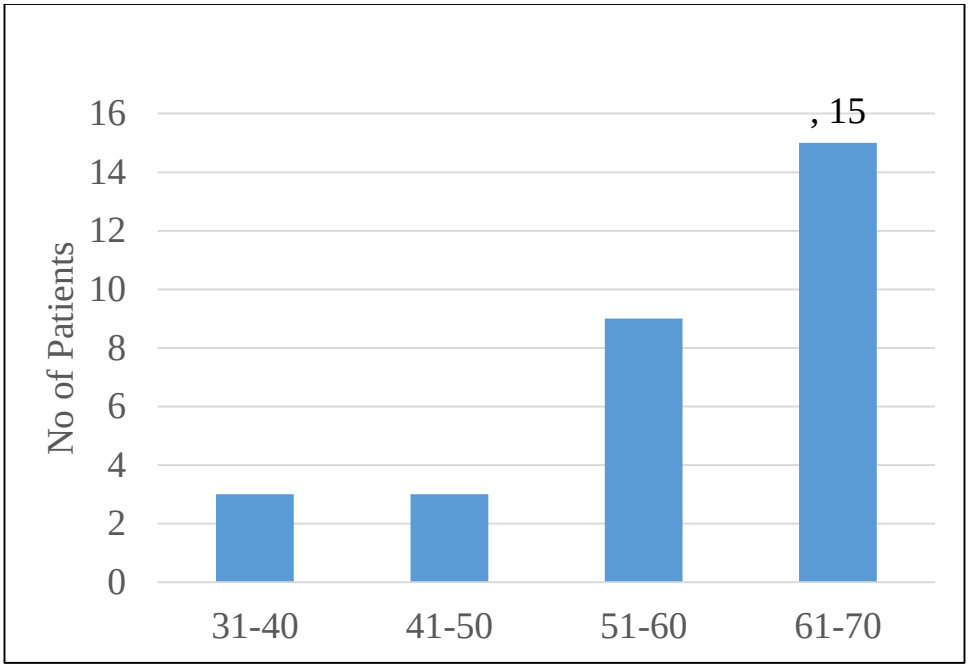
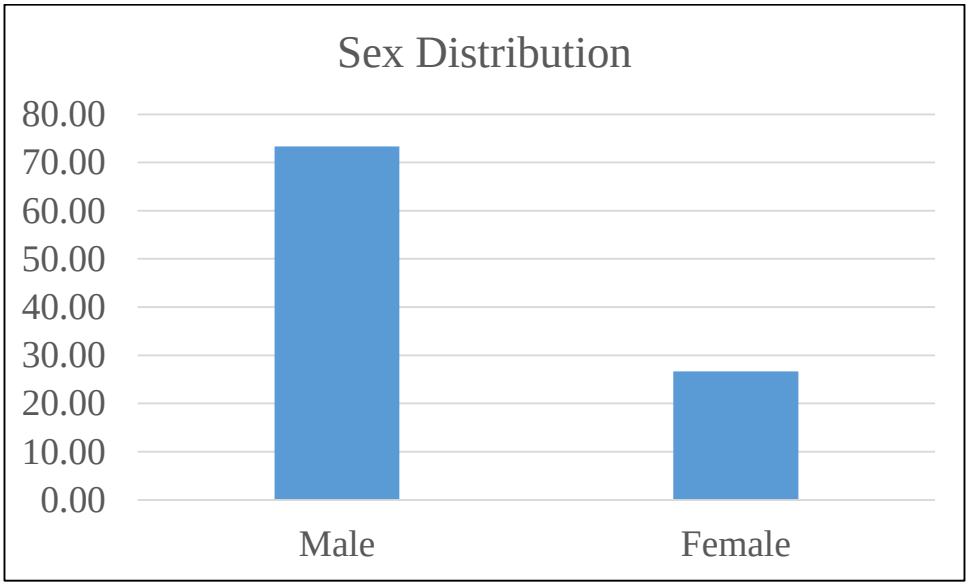


Figure 3: Sex Distribution



3. Performance Status (Table 3):

All the patients selected in this study had a performance status of 3 or worse at presentation as measured by ECOG classification.

Performance Status	Count	Percentage Population
II	0	-
III	20	66.67
IV	10	33.33

4. Staging:

a. Stage Grouping (Table 4):

Of the 30 patients, 13 belonged to locally advanced stage while 17 patients belonged to the very advanced stage.

Stage Grouping	Count	Percentage Population
IV A	13	43.33
IV B	17	56.67

Figure 4: Performance Status

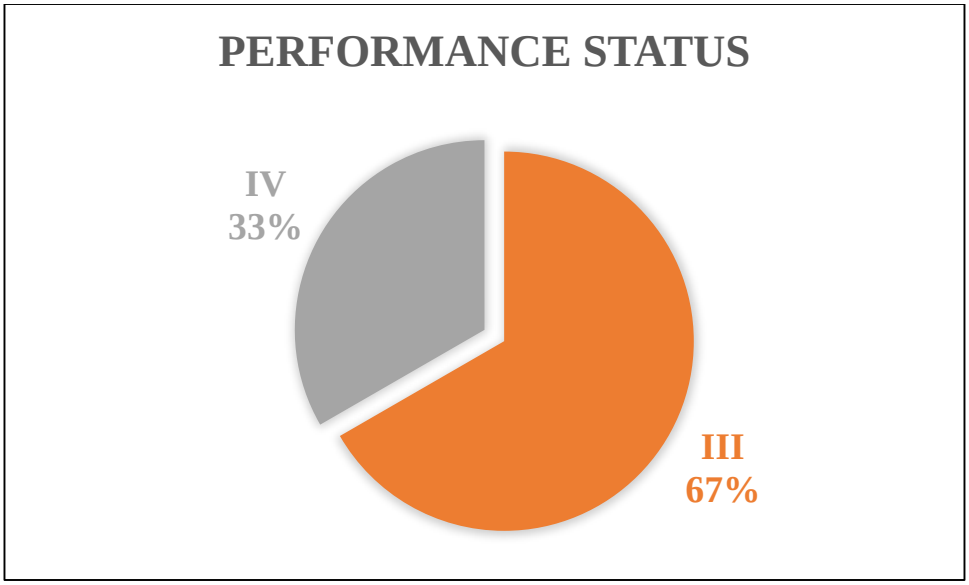
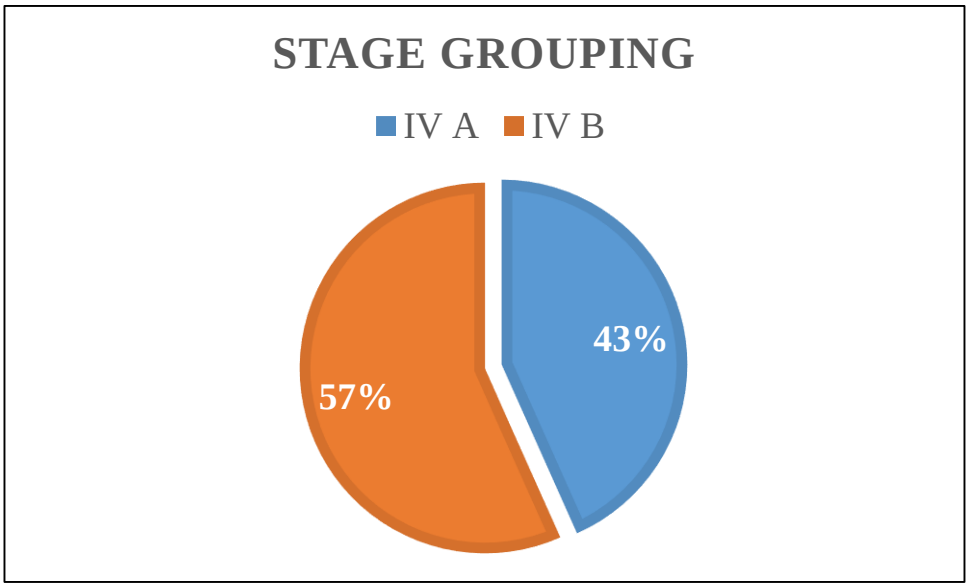


Figure 5:Stage Grouping



b. Nodal Stage at Presentation:

Stage IV B comprised 56.67% of the population and N3 node (node size more than 6 cm) at presentation was seen in 46.67% of the cases (n=14). One patient had bilateral cervical lymphadenopathy of 7 to 8 cm while one other patient had a neck node of 13 cm, measured in the longest axis.

c. Stage Distribution (Table 5):

The stage distribution of the study population was as follows:

Stage Distribution				
Tumour/ Node	**N1**	**N2**	**N3**	**Total**
T2	0	3	3	6
T3	0	0	3	3
T4a	0	10	7	17
T4b	2	1	1	4

5. **Histological Differentiation:** Histological differentiation was well differentiated in 11 (36.67%), moderate in 16 (53.33%) and poorly differentiated squamous cell carcinoma in 3 (10%).

Figure 6: Stage Distribution

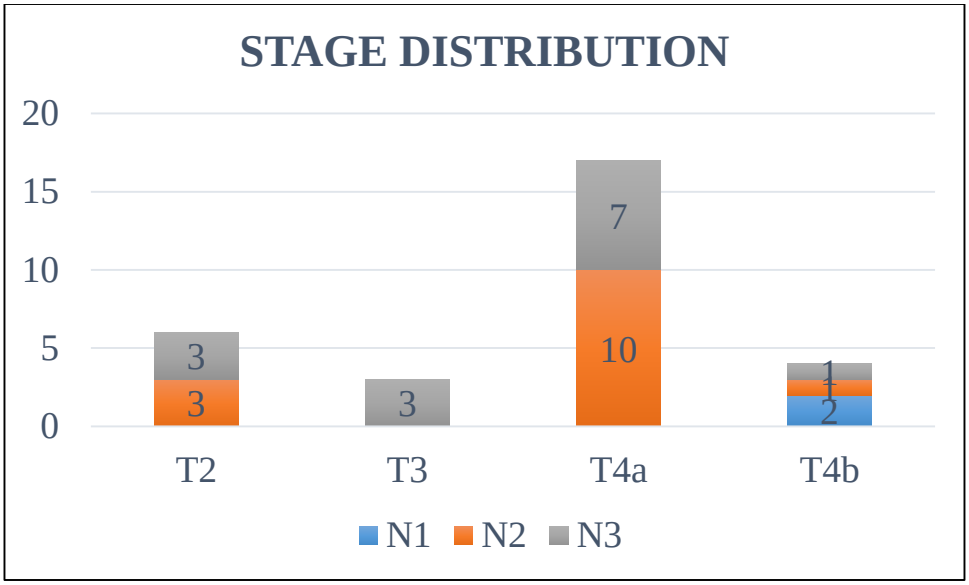
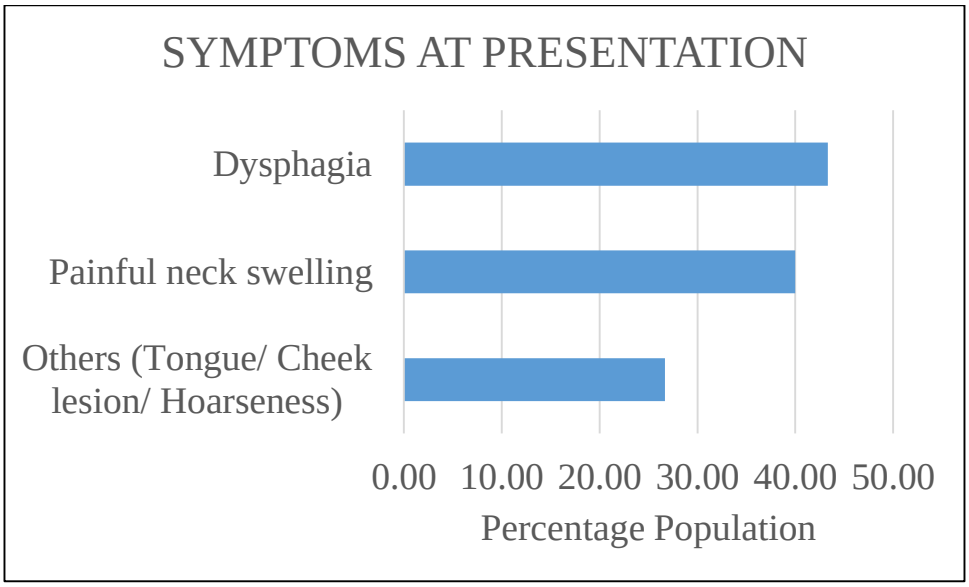


Figure 7: Symptoms at Presentation



6. Symptoms at Presentation (Table 6):

Symptoms At Diagnosis	Count	Percentage Population
Painful neck swelling	12	40.00
Dysphagia	13	43.33
Others (Tongue/ Cheek lesion/ Hoarseness)	8	26.67

More than one symptom at presentation was seen in 12 (40%) of the patients.

7. Sites of Primary Tumour (Table 7):

Sites	Count	Percentage Population
Oral Cavity	8	26.67
Oropharynx	10	33.33
Larynx	4	13.33
Hypopharynx	8	26.67

Figure 8: Site of Primary Tumour

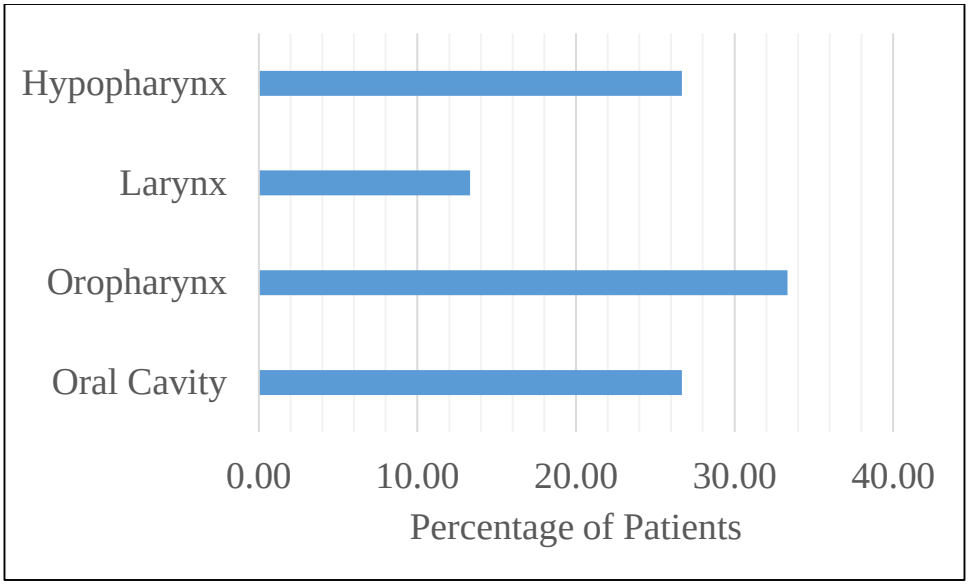
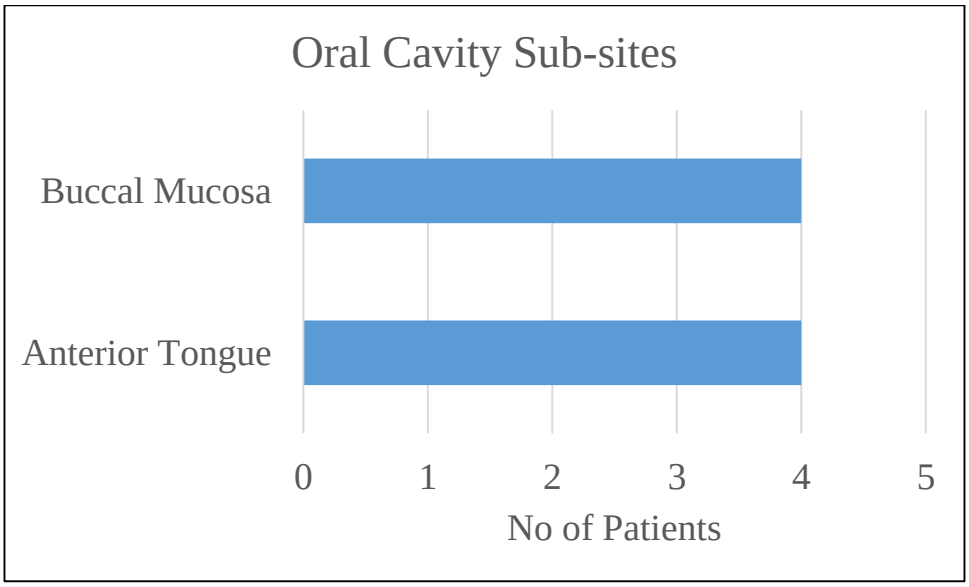


Figure 9: Oral Cavity Sub-sites



a. Oral Cavity Sub-sites (Table 8):

The oral cavity tumours consisted of anterior tongue and buccal mucosa with equal frequency. None of the cases had primary of the lip or floor of mouth.

Oral Cavity Sub-sites	Count	Percentage Population
Anterior Tongue	4	13.33
Buccal Mucosa	4	13.33

b. Oropharyngeal Sub-sites (Table 9):

A wide variety of sub-sites were seen to be involved among the oropharyngeal primary tumours. However, base of tongue was the commonest sub – site, with a maximum of 20% patients of the total population.

Oropharynx Sub-sites	Count	Percentage Population
Base Of Tongue	6	20.00
Tonsillar Fossa	2	6.67
Vallecula	1	3.33
Posterior Pharyngeal Wall	1	3.33

Figure 10: Oropharyngeal Sub-sites

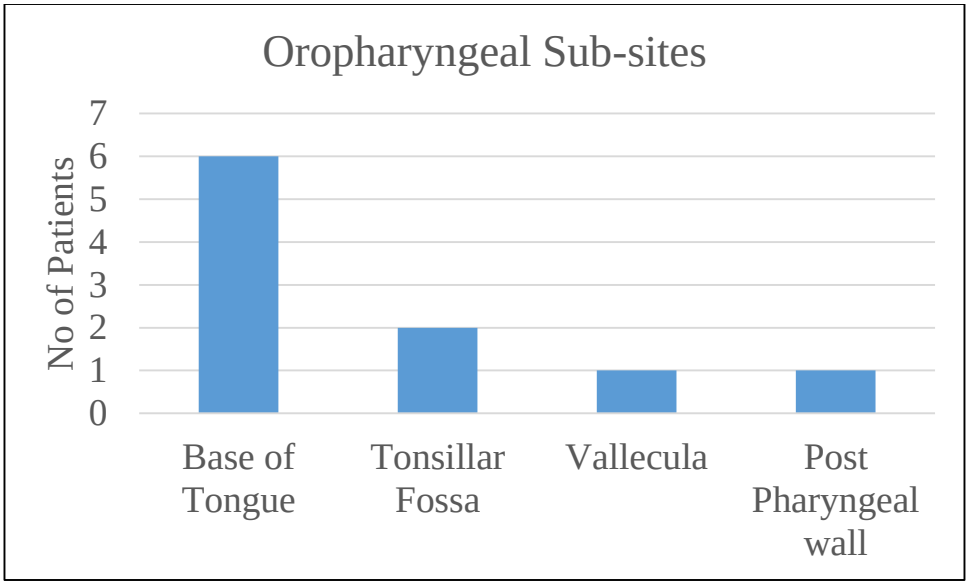
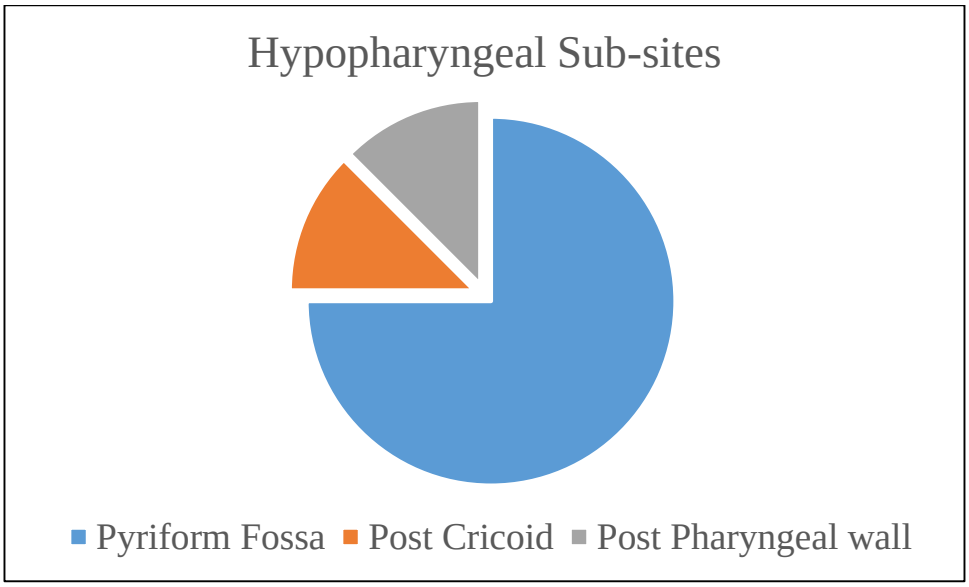


Figure 11: Hypopharyngeal Sub-sites



c. Laryngeal Sub-sites:

All four cases of laryngeal primaries were originating from the supra-glottic sub-site of Aryepiglottic fold. Right and left AE fold having equal incidence.

d. Hypopharyngeal Sub-sites (Table 10):

Hypopharyngeal Sub-sites	Count	Percentage Population
Pyriform Fossa	6	20.00
Post Cricoid	1	3.33
Posterior Pharyngeal Wall	1	3.33

Thus, Base of Tongue and Pyriform Fossa were the commonest sub- sites of primary tumour in this study.

8. Reason for Palliative Policy (Table 11):

Tumour stage alone was not the sole deciding factor for recruiting a patient under this protocol. Performance status, co-morbidities, expected survival, socio-economic factors were all taken into consideration.

Reason for Palliative RT Policy	Count	Percentage Population
Stage	12	40
Performance Status	13	43.33
Co-morbidities	5	16.67

9. Feeding Procedures:

Feeding procedures prior to initiation of radiotherapy are required in tumours of hypopharynx and oropharynx where the presenting symptoms are dysphagia. Otherwise, it can be inserted at symptom aggravation. In our study, nasogastric placement was required in 70% (n=21) of the patients at some point of treatment.

10. Number of RT Courses:

Twenty seven patients (90%) completed both the courses of radiation. That is, they achieved a BED of 56 Gy to the tumour. Out of the remaining 3, one defaulted for follow up after the first course, two had worsening of performance status along with aggravation of symptoms from co-morbidities and hence were deferred for the second course of radiation.

Figure 12: Reason for Palliative Policy

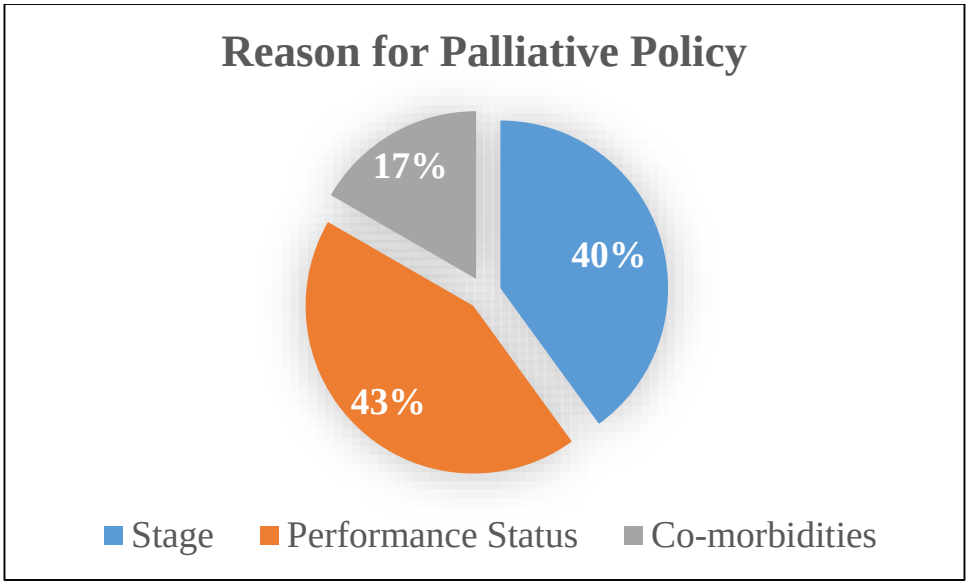
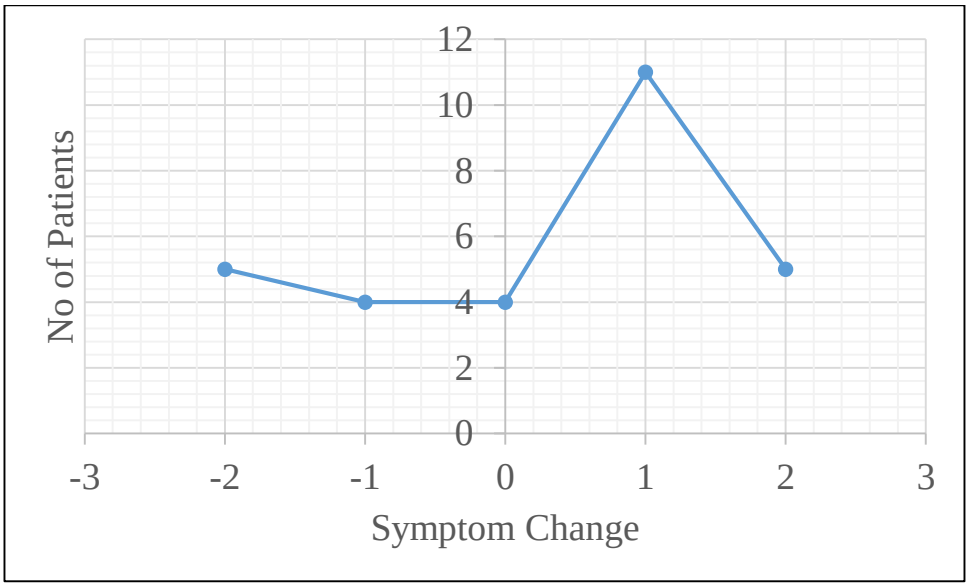


Figure 13: Symptom Change after First Radiation Course



11. Symptom Change after First Radiation Course (Table 12):

At the end of first course of radiation, contrary to the expectation, a majority of the patients (36.67%) experienced symptom aggravation in the form of dysphagia, pain or oedema over the pre-existent swelling. The symptom aggravation was mainly due to super added radiation toxicity to the pre-existing symptomatic disease.

Symptom Change after First Course Radiation	Count	Percentage Population
-2	5	16.67
-1	4	13.33
0	4	13.33
1+	11	36.67
2+	5	16.67

12. Toxicities out of First Radiation Course (Table 13):

Mucositis and dermatitis were the commonest toxicities observed after the delivery of first course of high dose radiation. No grade 3 toxicities of any kind were observed among any of the treated patients. Few cases experienced grade 1 to 2 laryngeal/ pharyngeal toxicities.

First Radiation Course Toxicity	No of Patients			
	Skin Toxicity	Mucositis	Laryngitis	Pharyngitis
No toxicity	0	13	21	15
Grade 1	26	1	4	7
Grade 2	3	15	4	7
Grade 3	0	0	0	0

13. Response out of First Radiation Course (Table 14):

At the second week follow up, only a minimal response was observed in majority of the patients while 6 patients had a partial response.

Response After First Course Radiation	Count	Percentage Population
Minimal	18	60.00
Partial	6	20.00
Not Assessable	6	20.00

Figure 14: Toxicities out of First Radiation Course

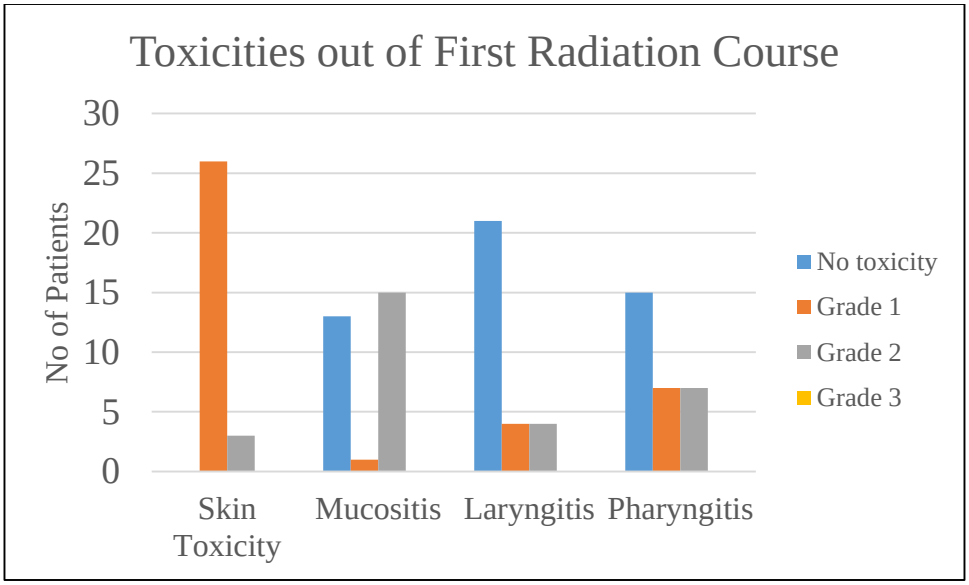
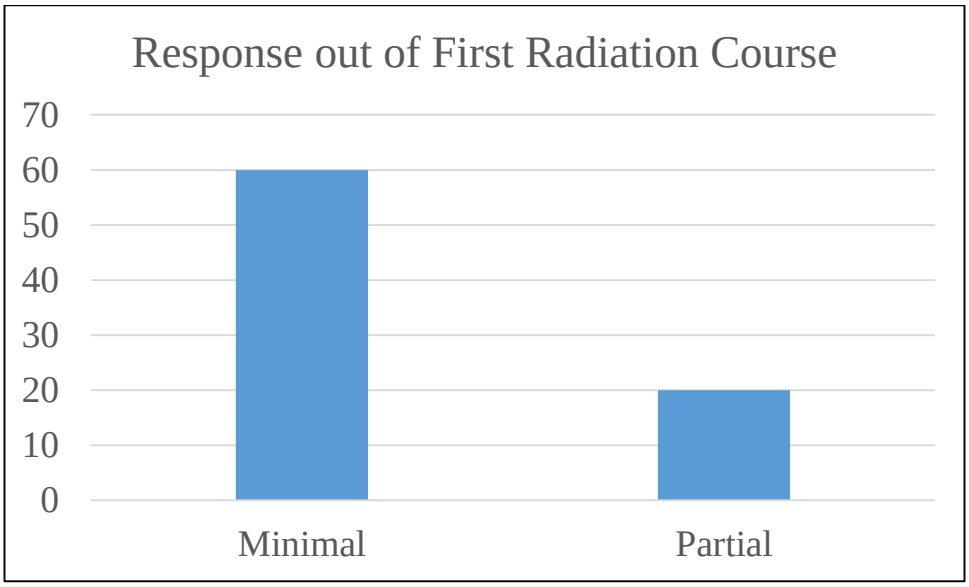


Figure 15: Response out of First Radiation Course



14. Symptom Relief at First month Follow-up (Table 15):

At first follow up after completion of treatment course, 73.33 % patients experienced symptomatic improvement. Three patients did not have any change in symptoms while two patients had symptom worsening post-treatment.

Symptom Change At First Follow Up	Count	Percentage Population
-2	10	33.33
-1	12	40.00
0	3	10.00
1+	2	6.67
2+	0	0.00

15. Toxicities at First month Follow-up (Table 16):

At the first follow up after completion of treatment, definite signs of treatment toxicity were observed in all patients. Majority of the patients had some form of grade 2 toxicity. Five patients also experienced grade 3 pharyngitis.

Figure 16: Symptom Change at First Month Follow Up

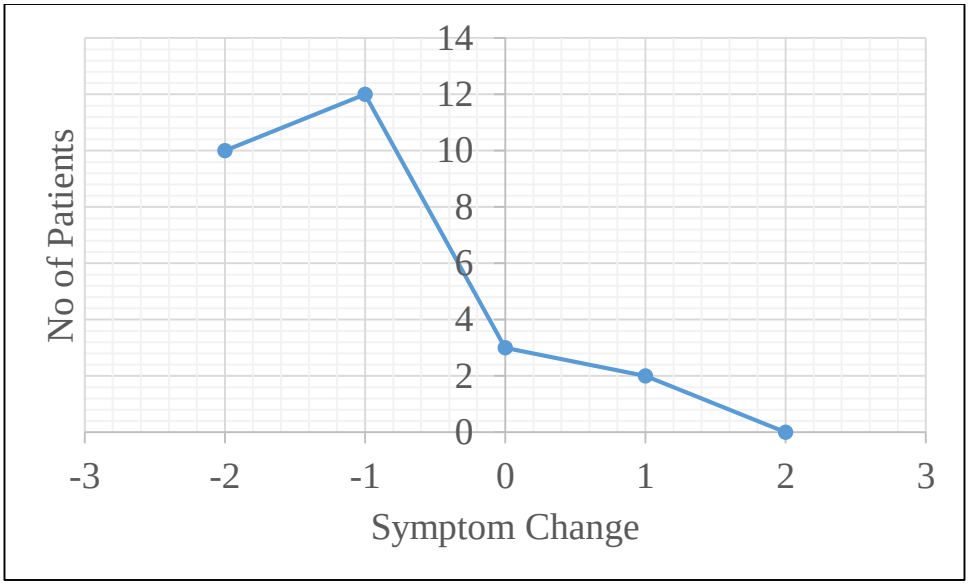
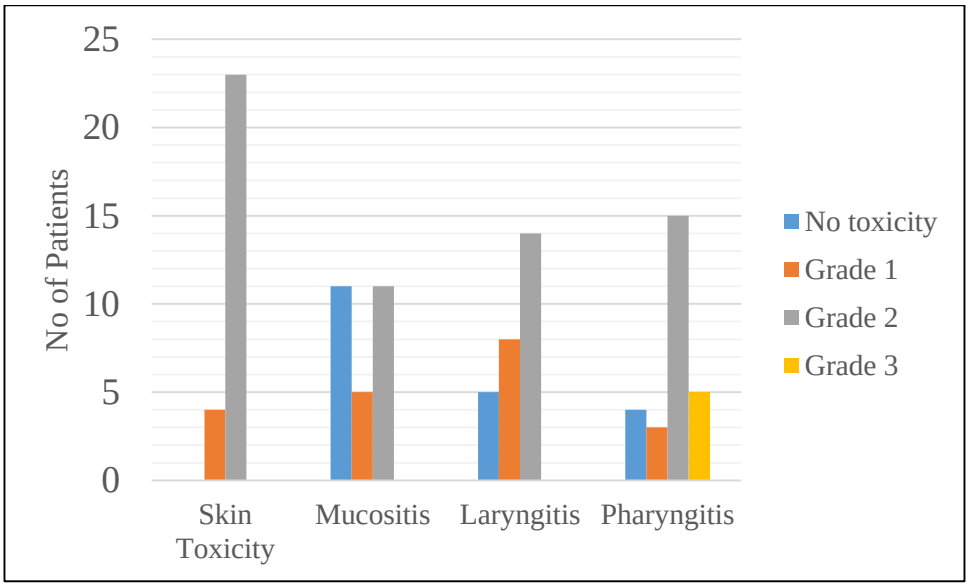


Figure 17: Toxicities at First Month Follow Up



Toxicity at First Month Follow Up	No of Patients			
	Skin Toxicity	Mucositis	Laryngitis	Pharyngitis
No toxicity	0	11	5	4
Grade 1	4	5	8	3
Grade 2	23	11	14	15
Grade 3	0	0	0	5

16. Response at First month Follow-up (Table 17):

At the end of first month from treatment completion, partial response was seen in 80% of the cases. No complete responses were observed. Minimal residue was seen in three cases.

Response At First Month Follow Up	Count	Percentage Population
Minimal Residual Disease	3	10.00
Partial	24	80.00

Figure 18: Response at First Month Follow Up

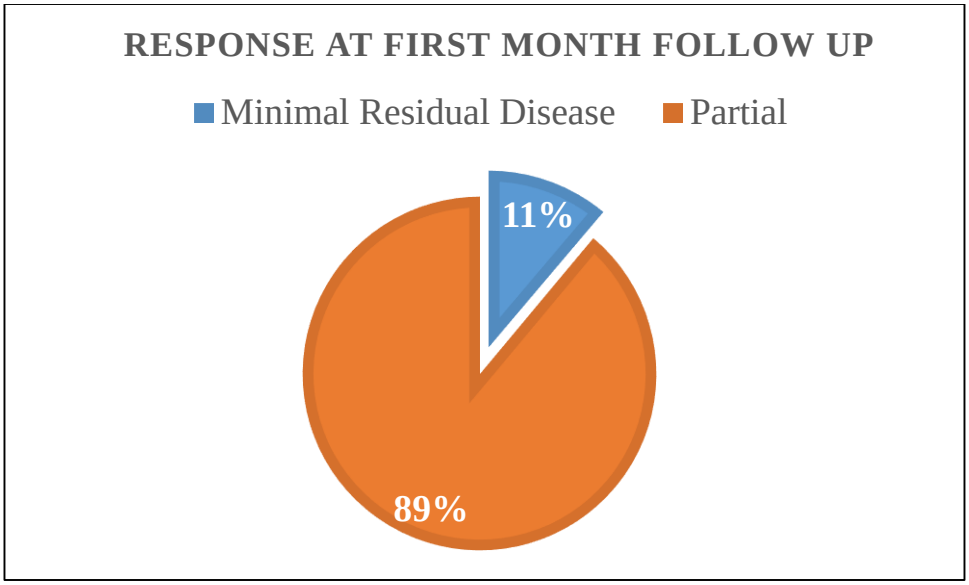
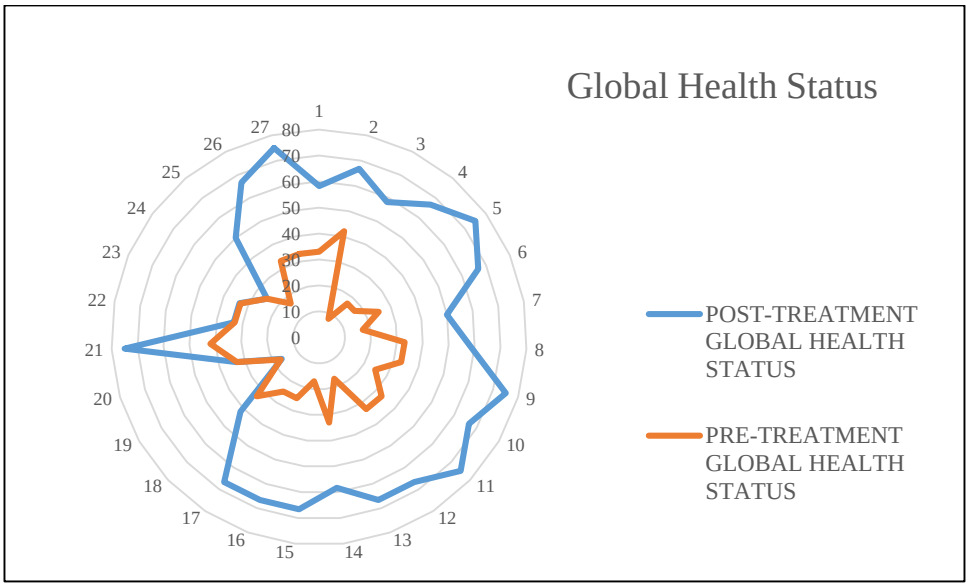


Figure 19: Global Health Status

(Transformed Scores)



17. Quality of Life Scores:

The quality of life scores were assessed using the EORTC QLQ-30. It is a 30 point patient (self-scoring) questionnaire. It assesses Global health status with 2 points, Functional scores with 15 points and Symptom scale with 13 points.

a. Global Health Status (Table 18):

The median pre-treatment Global health status score was 33 (observed range: 8 – 42). The possible data range can be from 0 – 100. Representing, zero as a very poor score and 100 as the best possible self-assessment of health status. The improvement after completion of treatment was observed as the post-treatment median Global Health scores was computed to be 67. The median improvement in scores was by 34.

Pre- treatment Global Health Score	Post treatment Global Health Score	Improvement in Global Health Score	Data Range
33	67	34	0-100

b. Functional Scales (Table 19):

The summated and raw scores of functional scales were calculated. The pre – treatment median summated score for the study group was 35 while raw score was 2. The summated score may vary from 15 – 60 while raw score has the range of 1 – 4. Higher the functional score, better is the quality of life.

Functional Scores	No of Patients (Pre-treatment)	No of Patients (Post-treatment)
<50	10	2
51-60	11	9
61-70	5	11
>70	1	5

Thus, an improvement was observed in the post – treatment functional scores, as number of patients getting higher scores increased. The median improvement observed was by a score of 7.

c. Symptom Scales:

The symptoms assessed were fatigue, nausea & vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and financial difficulties. The median pre – treatment scores for each were:

i. Fatigue – 8 /12
ii. Nausea/ Vomiting – 2 /8
iii. Pain – 6 /8
iv. Dyspnoea – 2 /4
v. Insomnia – 2 /4
vi. Loss of Appetite – 2 /4
vii. Constipation – 1 /4
viii. Diarrhoea – 1 /4
ix. Financial Hardships – 3 /4

The median raw score was 2 while median summated score was 36. The summated score may vary from 13 – 52 while raw scores may vary from the 1 – 4. The median post – treatment summated score was 28. Thus, the median improvement in symptom score was measured to be (-7). As the scores on the symptom scale decrease, the improvement is measured as negative. One patient had no change in

Figure 20: Functional Scales

(Transformed Scores)

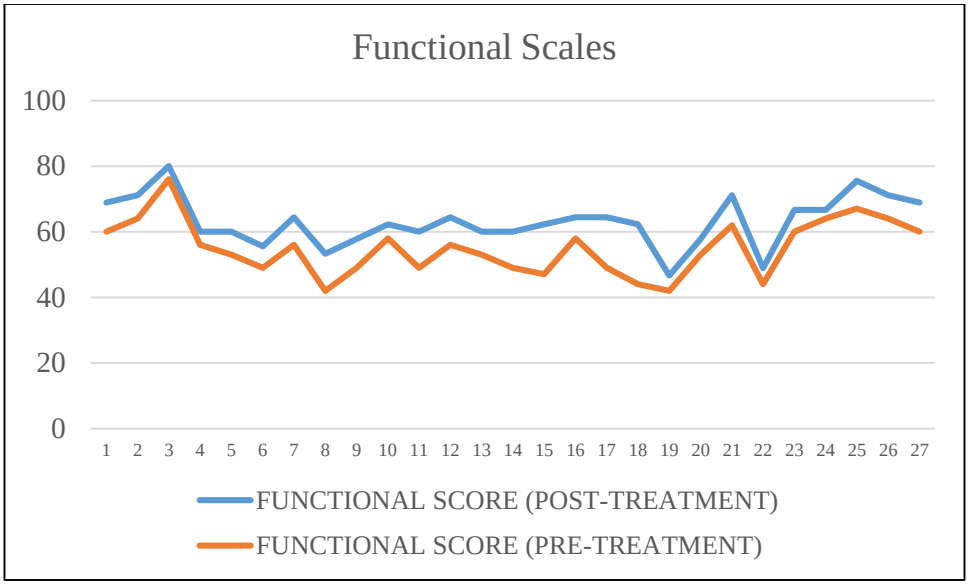
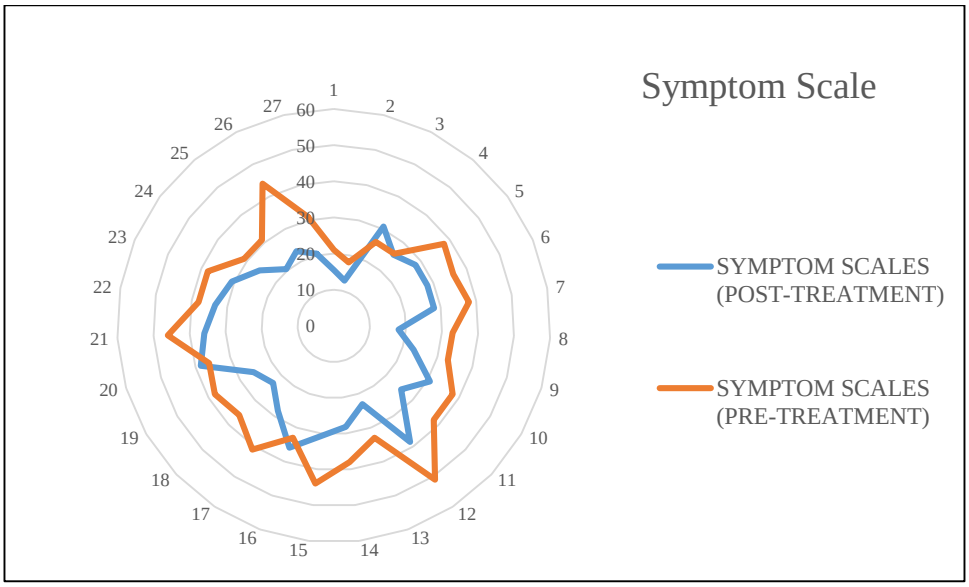


Figure 21: Symptom Scales

(Transformed Scores)



scores while two patients had a positive improvement in symptom score indicating symptom progression post treatment.

18.Response Duration:

Median duration of response of the patients treated with this protocol was 2 months post-completion of treatment. Maximum response duration observed was 3 months. Progression was seen in local disease for 11 patients (36.67%), loco-regionally for 11 patients (36.67%) and regional progression in 6 (20%) cases.

DISCUSSION

DISCUSSION

The standard of care for unresectable head and neck cancer is concurrent chemoradiation with radiotherapy given up to 70 Gy (2 Gy/ fraction) along with Cisplatin 100mg/ m^2 on Day 1, 22 and 43. However, this treatment is applicable to young patients with an ECOG performance status of 0 – 2, good expected survival and whom the radical treatment is likely to achieve a cure. Patients not fulfilling these pre-requisites for a radical treatment are more likely to go for palliation. Due to absence of guidelines or evidence base for palliative regimen dose, schedules and fractionations, patients are treated largely on the basis of traditional individualised institutional protocols.

Thus, this study protocol was formulated to determine the efficacy and feasibility of split-course hypofractionated palliative radiation among our patient population. Overviewing the results, the primary objective and goals of this study can be said to be achieved.

Our study population showed demographic trend towards the higher age group. Median age was 61 years. Almost 80% of the population was above 50 years of age with 30% being above 60 years. This may be

explained on the basis that, co-morbidity was one of the selection criteria for palliative treatment. As the age progresses, the likelihood of developing medical co-morbidities such as diabetes mellitus, systemic hypertension, coronary artery disease, cardiac conduction defects, renal and hepatic insufficiency increases.

The study group showed male predominance with only 27% patients being females. This was expected as the incidence of cancer is more in males in our country as they are more frequently exposed to carcinogens while at work, from habits of tobacco smoking or chewing, the use of pan masala and other risk taking behaviours. Also, rural females are less likely to report/ be taken to a tertiary cancer facility for treatment in time.

ECOG performance status at presentation was grade 3 or worse in all patients, as part of the inclusion criteria. Grade 3 performance status was in 67% of the cases while rest had grade 4. The NCCN guidelines for head and neck cancer recommend that patients of advanced stage with a good performance status of 0-2 should be given a trial of concurrent chemoradiation and attempted for cure and residual disease if any, should

be salvaged with surgical approach. Performance status in many studies has shown a correlation with treatment tolerance and outcome, thus a radical approach is not justified in patients with a poor PS.

The study had 57% of the patients in very advanced (IV B) stage while rest were in locally advanced stage (IV A). The patients with IV A disease were solely recruited on the basis of their performance status or co-morbidities. Among the 13 patients in stage IV A, three patients had stage T_2N_2 while 10 patients had stage $T_{4a}N_2$. All patients were deemed unresectable by the consultant surgical oncologist, during the institutional multi-disciplinary tumour board. Nodal stage of N_3 was seen in 14 out of 17 patients belonging to stage IV B. One patient with supraglottic primary at presentation had a matted nodal mass of 13 cm in the longest dimension, while one other patient with a T_2 base of tongue lesion, had bilateral nodal masses of 7 - 8 cm. The remaining patients had unilateral nodal masses ranging from 6 - 9 cm. These results thus corroborate the fact that our patients present in very advanced stages that are not amenable for any definitive modalities of treatment.

The different sites of primary tumours were oral cavity (27%), oropharynx (33%), larynx (13%) and hypopharynx (27%). Base of tongue (20%) and pyriform fossa (20%) were the commonest sub-sites of primary. It is known that base of tongue and pyriform fossa are among the sites of occult disease in head and neck cancer cases. Primary in these sub-sites can remain dormant for prolonged periods without much symptomatic manifestations. First symptoms at presentation in such cases is usually of bulky cervical nodal disease with occult primary. Only on detailed ENT examination and imaging, a primary is visualised at these sub-sites. Minor salivary glands, vallecula and nasopharynx are among the other sub-sites that can have a similar presentation.

Further, all laryngeal primaries were seen arising from the supraglottic structure, aryepiglottic fold. Supraglottis is the only part of larynx with richest lymphatic supply. The drainage is commonly seen into level II to level IV lymph nodes from tumours at this site while level Ib and level V being less common. The incidence of occult nodal disease can be seen in 16% of the cases at the time of elective neck dissection. Patients observed for a clinically negative neck eventually present with a positive nodal disease in 33% cases. [87, 88]

As mentioned above, stage was not the only criteria for selecting cases for palliative treatment. Poor performance status was the deciding factor for palliative course in 43% of the cases while 17% had co-morbidities such as renal insufficiency (2), long standing diabetes mellitus (2) and recent coronary event (1).

Histologically, all tumours were squamous cell carcinoma as per the inclusion criteria. Among them, majority were only moderately differentiated (53%) while 37% were well differentiated and 10% were poorly differentiated. Differentiation of a tumour has shown to have a definite relation to the treatment response. Poorly differentiated tumours show a good cytoreduction initially however, recurrences are frequent. Well differentiated tumours are known to have a lesser response to chemoradiation. As the cells are terminally differentiated, they are less likely to enter the cell cycle thus reducing the efficacy of chemotherapy and radiation.

Further, nutritional management was meticulously looked after in all cases. All patients who underwent a feeding procedure, received a nasogastric tube insertion. Nine of the 30 cases were intervened with a

feeding procedure before initiation of any treatment in view of severe dysphagia or excessive pre-treatment weight loss. The remaining 12 out of 21 cases received a feeding procedure during the course of treatment, mostly at the end of two week period. Dietary management was carried out for all patients. Those with feeding tube were given liquid to semi-liquid diet (chicken soups, raw eggs, kanji, milk, protein powder supplements, etc.) to compensate for the increased protein demand of cancer patients undergoing treatment.

Symptoms were recorded using the symptom assessment scale of 0 to 4. Dysphagia was the prime symptom among most of the patients (43%). Grade 3 dysphagia was observed in 9 patients while 4 patients had only grade 1 to 2 dysphagia. Painful neck swelling was the next common symptom with 40% presenting with this symptom. The matted nodal mass with hypoxic and necrotic areas, skin infiltration and neural infiltration causing mass effect over cervical structures resulted in the patients presenting with pain. About 40% patients had more than one symptom at the time of presentation.

After the first course of treatment, adequate symptom relief was observed in 30% of the patients. At least 37% of the cases had symptom worsening at the second week follow up after the first course. Symptom aggravation can be mainly attributed to the additive effect of radiation induced toxicities in pharynx or oral mucosa. Also, in patients with bulky cervical nodes, tumour lysis induced and vasogenic oedema post-irradiation resulted in aggravation/ inappreciable reduction in the size of nodal disease.

No mucosal or laryngo-pharyngeal toxicity was seen for 13, 21 and 15 number of patients respectively, of the patients treated. Commonest toxicity observed was grade 1-2 dermatitis and mucositis in 97% and 53% patients respectively. The first course of high dose radiation resulted in at least a minimal response in 60% of the tumours. Partial response was observed in 20% of the patients while disease status was not amenable for direct clinical assessment in 20%.

All patients received at least one course of radiotherapy. Only three patients could not be treated with the planned two courses of radiotherapy. One patient defaulted after the first course, while two

developed aggravation of symptoms from their co-morbidities and hence deferred from further treatment. No patient was deferred further course of treatment on grounds of tumour progression or excessive toxicity.

At the end of second course of treatment and the first month follow up, symptom relief was experienced by most of the patients (73%). Major improvement in symptom was noted in 33% while 40% experienced minor improvement. Only 7% (2 patients) had symptom worsening after the entire treatment course and 3 patients had no change in symptoms.

Toxicity profile was remarkable at the end of first month follow up. Skin toxicity of grade 1 – 2 was seen in all patients. Only 5 patients experienced a grade 3 pharyngitis. No other grade 3 toxicity was noted in any patient. No evidence of any toxicity in the mucosa, larynx and pharynx was noted in 11, 5 and 4 patients respectively. The improved toxicity profile was because of the 2 week gap period offered between the two courses of radiation. The gap allowed for normal tissue recovery which minimised the toxicity of the regimen.

Response evaluation at the end of one month showed an overall response rates of 100% with only a minimal residual disease among 3 patients. All the other patients achieved a partial response from this treatment regimen. The response was maintained for a median duration of 2 months. Six patients were free from tumour progression for a period of 3 months.

This study had a major advantage in the form of quality of life assessment and its comparison pre and post-treatment. The scores were assessed using a patient rated questionnaire, the EORTC QLQ-30. This questionnaire has a 30 point scoring system and has three elements namely, the Global health status, functional scales and symptom scales. Global health status has two items (questions) for assessment and the range of answers is 6, with a maximum score of 7 and minimum of one. Functional scales have 15 items (questions) for assessment with maximum score of 4 and minimum of one, thus the range of responses being three. Similarly, symptom scales assess for 13 items with maximum and minimum scores of 4 and 1. Range of symptom scales is 3.

The pre – treatment Global health score was found to have a median of 33. With the maximum and minimum scores of 100 to 0, no patient had a score of more than 42. Hence, it is evident that all patients rated their overall state of health as poor at the time of presentation considering the presence of advanced disease which resulted in distressing symptoms and compromised the nutritional status. In the post – treatment assessment, the median score was found to be 67, thus giving a median improvement in overall health status by a score of 34.

Among the functional scales, the items assessed were for categories of physical functioning, role functioning, emotional, cognitive and social functioning. The median summated score was 35 (out of 60) while the median raw score (RS) and the median transformed score were 2 (out of 4) and 56 (out of 100) respectively. The median scoring of individual categories was 14 (out of 20) for physical, 5 (out of 8) for role, 7 (out of 16) for emotional, 4 (out of 8) for cognitive and 5 (out of 8) for social functions. Higher the summated score, more is the functional impairment thus, patients had a major compromise of their physical activity and the disease was responsible for a major emotional burden on their functioning. The cognitive and social abilities were largely

unaffected. The scores showed an improvement post – treatment with the median transformed score of 62. Maximum improvement was seen in physical and emotional functions as they showed low score at the time of presentation.

Symptom scales were scored for fatigue, nausea & vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and financial difficulties. The median pre – treatment summated score was 27 (out of 52) while the raw score and transformed score were 2 (out of 4) and 36 (out of 100) respectively. The median scores of individual symptom categories were 8 (out of 12) for fatigue, 2 (out of 8) for nausea & vomiting, 6 (out of 8) for pain, 2 (out of 4) for dyspnoea, 2 (out of 4) for insomnia, 2 (out of 4) for loss of appetite, 2 (out of 4) for constipation, 2 (out of 4) for diarrhoea and 3 (out of 4) for financial difficulties. Thus, financial burdens related to daily wages, cost of treatment and future financial issues of the family were largely worrisome for the patient. The patient rated quality of life symptom scale scores correlate well with the physician recorded symptom assessment scale at the time of presentation. Post – treatment, improvements were recorded in the pain scores and

fatigue scores. No major improvements were observed in the other scores as scored on the first month follow up.

Overview of present study and available literature on palliative radiotherapy (Table 20)

Author/ Reference	Patient Characteristics	Radiation Schedule	Symptom control	Treatment Response	Toxicities
Present Study	30 Patients, Median age 61, PS >2 100%, Stage IV 100%	2 courses of 20 Gy in 5 fractions, 2 week gap between courses	Overall symptom improve-ment 73%, QoL improve-ment 34%	Overall Response rate 100%: Minimal residue in 10%, PR 80%	G3 pharyngi-tis 16%, G2 mucositis 37%, G2 laryngitis 47%
Agarwal et al [45]	110 Patients, Median age 55, Stage IV 95%	40 Gy in 16 fractions, further 10 Gy if good response	Less than 50% in 26%, more than 75% in 17%	CR 10%, PR 63%, SD 16%	G3 Skin 14%, Mucositis G3 63%, G4 3%

Minatel et al [80]	58 Patients, Median age 67, PS 60 (KPS), Stage IV 79%	2 courses 25 Gy/ 10 fractions, 2 weeks gap, with bleo-mycin	Overall symptom relief 81%	CR 28%, PR 41%, SD 21%, PD 10%	G3 Mucositis 46%, G3 Dys-phagia 3.4%
Mohanti et al [43]	352 Patients, Median age 55, Stage IV 100%	20 Gy in 5 frac, further up to 70Gy if good response after 4 wk	Pain >50% in 57% Dys-phagia >50% in 53%	At one month, 37% PR	At one month, 100% patchy mucositis
Corry et al [85]	30 Patients, Median age 73, PS>2 66%, Stage IV 97%	3 courses of 14 Gy in 4 fractions, 2 per day, 4 week gap between courses	Pain 56% Dys-phagia 33%, QoL improve-ment 44%	Overall response 53%	Grade 3 mucositis 0%
Porceddu et al [82]	35 Patients, Median age 68, PS>2 29%, Stage IV 65%	30 Gy/ 5 fractions, 2 per week. 6 Gy boost in selected patients	Pain 67%, QoL improve-ment 62%	Overall response 80%	Grade 3 mucosits 26%, dys-phagia 11%, skin 11%

Kancherla et al [86]	33 Patients, Median age 76, PS>2 58%, Stage IV 91%	2 courses for total 40 Gy in 10 fractions, 2 week gap	Overall response 79%	CR 39%, PR 33%, SD 21%, PD 6%	Grade 3 mucositis 6%, skin 3%, dys-phagia 9%

Thus, the results of our study are similar to the studies available in literature over palliative head and neck cancer irradiation. A lower rate of acute toxicity along with an overall response rate of 100% are the added advantages noted in our study.

Merits of the Study:

a. Short, split – course of radiation was delivered, beneficial in a resource strained country and convenience of the patient
b. Toxicities were meticulously watched for and incidence of grade 3 toxicity was minimal.
c. Two week gap allowed patient's recovery
d. Good symptom relief achieved
e. Quality of Life scores improved adequately

f. Response was observed for a good length of time without disease or symptom progression.
g. Treated all the patients with poor performance status, very advanced stage of the disease or co-existing co-morbidities which are usually offered only best supportive care.

De-Merits of the Study:

a. Single arm, Phase II study
b. Due to smaller sample size, significance of the results could not be derived.
c. Long term follow up was not ensued, ergo late consequences of high dose radiation could not be commented upon.
d. High dose of radiation itself caused initial symptom aggravation in a sizeable number of patients.

Future Directions:

a. Larger, multi-centric randomised controlled trial to prove the efficacy of this regimen over other palliative regimens in a diverse population of patients would be needed.

b. Long term follow up of patients to evaluate the late complications as well as to study the survival patterns and benefits.

c. Establishing the patient related factors or selection criteria for differentiating patients suitable for palliative treatment from those amenable for radical approach.

CONCLUSIONS

CONCLUSION

Thus, in the given scenario of Indian patient population of head and neck squamous cell carcinoma, where patients usually present in the locally advanced stages, the treatment plan depends largely on patient factors such as age, performance status, tumour extent and resectability and socio-economic factors. In patients having advanced age, poor performance status with advanced, unresectable cancer, cure is a distant reality and is rarely achievable even with all the recent developments in radiation technology or chemotherapeutic or targeted agents.

This study hence achieved its objectives of showing that such patients are suitable for treatment under split-course hypofractionated radiotherapy. This regimen provided appropriate symptom relief (73% cases) and improvement in quality of life, with adequate tumour response maintained for a prolonged period along with manageable acute toxicities.

BIBLIOGRAPHY

BIBLIOGRAPHY:

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F (2013). GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC
2. Bray F, Ren JS, Masuyer E, Ferlay J (2013). Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer, 132(5):1133–1145.
3. Dikshit R. et al. Cancer mortality in India: a nationally representative survey. The Lancet 2012; 6736(12): 60358-4.
4. Sinha DN, Gupta PC, Dobe M, Prasad VM. Tobacco control in schools of India: review from Global School Personnel Survey 2006. Indian J Public Health. 2007 Apr-Jun; 51(2):101-6.
5. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55:74.
6. Chaturvedi P. Head and neck surgery. J Can Res Ther 2009; 5:143.
7. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63:11.
8. Sankaranarayanan R, Masuyer E, Swaminathan R, et al. Head and neck cancer: a global perspective on epidemiology and prognosis. Anticancer Res 1998; 18:4779.

9. Noronha V, Tsomo U, Jamshed A, Hai MA, Wattegama S, Baral RP, Piya M, Prabhash K. A fresh look at oncology facts on south central Asia and SAARC countries. South Asian J Cancer 2012; 1:1-4
10. Boyle P, Macfarlane GJ, Scully C. Oral cancer: Necessity for prevention strategies. Lancer 1993; 342(8880):1129.
11. 18 Kurumatani N, et al. Time trends in the mortality rates for tobacco and alcohol related cancers within the oral cavity and pharynx in Japan, 1950-94. J Epidemiol 1999; 9(1):46-52.
12. 19 Macfarlane GJ, et al. Alcohol, tobacco, diet and the risk of oral cancer: a pooled analysis of three case-control studies. Eur J Cancer B Oral Oncol 1995; 31B (3):181-187.
13. Lambert R, et al. Epidemiology of cancer from the oral cavity and oropharynx. Eur J GastroenterolHepatol 2011; 23(8):633-641.
14. Browman GP, Wong G, Hodson I, et al. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Engl J Med 1993; 328(3):159.
15. Talamini R.; LA Vecchia C.; Levi F.et.al. Cancer of the oral cavity and pharynx in nonsmokers who drink alcohol and in nondrinkers who smoke tobacco. Journal of the N Engl J Med; 344.

16. Zheng T.Z., Boyle P., Hu H.F.et. al. Tobacco smoking, alcohol consumption, and risk of oral cancer: A case-control study in Beijing, People's Republic of China. Cancer Causes and Control 1990; 1:173–9.
17. Bagnardi V., Blangiardo M., LA Vecchia, C., Corrao G. A meta-analysis of alcohol drinking and cancer risk. British Journal of Cancer 2001; 85:1700– 5.
18. Mork J, LIE A.K, Glattre E, Hallmans G, Jellum E, KoskelaP.Human Papillomavirus Infection As A Risk Factor For Squamous-Cell Carcinoma Of The Head And Neck. National Cancer Institute 2001; 90:1901–1903.
19. Paz IB, Cook N, Maryon, Yuan Xie, Wilczynski SP. Human Papillomavirus (HPV) in Head and Neck Cancer An Association of HPV 16 with Squamous Cell Carcinoma of Waldeyer's Tonsillar Ring. CANCER 1997; 79: 3.
20. Gillison ML, Koch MW, Capone RB, Spafford M, Westra W, Li Wu et al. Evidence for a Causal Association Between HCamille C.R. Ragin and EmanuelaTaioli. Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: Review and meta-analysis. Int. J. Cancer 2007; 121:1813–20.
21. Human Papillomavirus and a Subset of Head and Neck Cancers. Journal of the National Cancer Institute 2000; 92:9.

22. Foulkes WD, Brunet JS, Sieh W, Black MJ, Shenouda G, Narod SA. Familial risks of squamous cell carcinoma of the head and neck: retrospective case-control study. BMJ 1996; 313:716.

23. Papadimitrakopoulou V, Izzo J, Lippman SM, et al. Frequent inactivation of p16INK4a in oral premalignant lesions. Oncogene 1997;14:1799.

24. Hollstein M, Sidransky D, Vogelstein B, Harris CC. p53 mutations in human cancers. Science 1991; 253:49.

25. Callender T, el-Naggar AK, Lee MS, Frankenthaler R, Luna MA, Batsakis JG. PRAD-1 (CCND1)/cyclin D1 oncogene amplification in primary head and neck squamous cell carcinoma. Cancer 1994;74:152.

26. Okami K, Reed AL, Cairns P, et al. Cyclin D1 amplification is independent of p16 inactivation in head and neck squamous cell carcinoma. Oncogene 1999; 18:3541.

27. Cully M, You H, Levine AJ, Mak TW. Beyond PTEN mutations: the PI3K pathway as an integrator of multiple inputs during tumorigenesis. Nat Rev Cancer 2006; 6:184.

28. Hennessy BT, Smith DL, Ram PT, Lu Y, Mills GB. Exploiting the PI3K/AKT pathway for cancer drug discovery. Nat Rev Drug Discov 2005; 4:988.

29. Kalyankrishna S, Grandis JR. Epidermal growth factor receptor biology in head and neck cancer. J ClinOncol 2006; 24:2666.

30. Rogers SJ, Harrington KJ, Rhys-Evans P, O-Charoenrat P, Eccles SA. Biological significance of c-erbB family oncogenes in head and neck cancer. Cancer Metastasis Rev 2005; 24:47.

31. Bentzen SM, Atasoy BM, Daley FM, et al. Epidermal growth factor receptor expression in pretreatment biopsies from head and neck squamous cell carcinoma as a predictive factor for a benefit from accelerated radiation therapy in a randomized controlled trial. J ClinOncol 2005; 23:5560.

32. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006; 354:567.

33. Simon J, Stewart W, E. E. C., Lisa Licitra, et al. A Phase III randomized parallel-group study of gefitinib (IRESSA) versus methotrexate (IMEX) in patients with recurrent squamous cell carcinoma of the head and neck. Proceedings of the American Association for Cancer Research Annual Meeting, A3522, 2007.

34. Werness BA, Levine AJ, Howley PM. Association of human papillomavirus types 16 and 18 E6 proteins with p53. Science 1990; 248:76.

35. Wilczynski SP, Lin BT, Xie Y, Paz IB. Detection of human papillomavirus DNA and oncoprotein overexpression are associated with distinct morphological patterns of tonsillar squamous cell carcinoma. Am J Pathol 1998; 152:145.

36. Oda D, Bigler L, Lee P, Blanton R. HPV immortalization of human oral epithelial cells: a model for carcinogenesis. Exp Cell Res 1996; 226:164.

37. Chen AY, Myers JN. Cancer of the oral cavity. Dis Mon 2001; 47(7):275-361.

38. Myers JN, Greenberg JS, Mo V, et al. Extracapsular spread. A significant predictor of treatment failure in patients with squamous cell carcinoma of the tongue. Cancer 2001; 92:3030-36.

39. Johnson JT, Barnes EL, Myers EN, et al. The extracapsular spread of tumors in cervical node metastasis. Arch Otolaryngol 1981; 107:725-29.

40. Pignon JP, le Maître A, Maillard E, et al: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC). An update on 93 randomised trials and 17,346 patients, RadiotherOncol 92:4-14, 2009.

41. Murdoch-Kinch CA, Zwetchkenbaum S. Dental management of the head and neck cancer patient treated with radiation therapy. J Mich Dent Assoc 2011; 93: 28-37.
42. Epstein JB, Thariat J, Bensadoun RJ, et al. Oral complications of cancer and cancer therapy: from cancer treatment to survivorship. CA Cancer J Clin 2012; 62: 400-422.
43. Mohanti BK, Umapathy H, Bahadur S, Thakar A, Pathy S. Short course of palliative radiotherapy of 20Gy in 5 fractions for advanced and incurable head and neck cancer: AIMS study. RadiotherOncol 2004;71:275-80.
44. Kumar .S, Heller RF, Panday V, Tewari V, Bala N, Oanh KT.Delay in presentation of oral cancer, a multi factor analytical study. Natl Med J India 2001; 14(1):15 -17.
45. Jai Prakash Agarwal. Hypofractionated, palliative radiotherapy for advanced head and neck cancer RadiotherOncol 2008; 89:51-56.
46. KaustavTalapatra, Tejpal Gupta, Jai Prakash Agarwal, et al. Palliative radiotherapy in head and neck cancers: Evidence based review; Indian journal of palliative care 2006; 12(2): 44-50.
47. Weissberg JB, Pillsbury H, Sasaki CT, Son YH, Fischer JJ. High fractional dose irradiation of advanced head and neck cancer.Implications

for combined radiotherapy and surgery. Arch Otolaryngol 1983; 109:98-102.

48. Bentzen SM, Saunders MI, Dische S, Bond SJ. Radiotherapy relatedearly morbidity in head and neck cancer: quantitative clinical radiobiology asdeduced from the CHART trial. RadiotherOncol 2001; 60(2):123-135.

49. ANG K. K., Xu F. X., Vanuytsel L. and Van Der Schueren E. Repopulation kinetics in irradiated mouse lip mucosa. The relative importance of treatment protraction and time distribution of irradiation. Radiat. Res 1989; 101: 162-169.

50. W.H. Bragg and R. Kleeman. On the ionization curves of radium. Philosophical Magazine S6 (1904), 726-738.

51. Vlacich G, et al. Dose to the inferior pharyngeal constrictor predicts prolonged gastrostomy tube dependence with concurrent intensity-modulated radiation therapy and chemotherapy for locally-advanced head and neck cancer.RadiotherOncol 2014;110(3):435-40.

52. Farach, A.M. et al.Chronic Dysphagia after IMRT/Chemotherapy is Associated with Higher Mean Pharyngeal Constrictor Dose. Int J RadiatOncolBiolPhys 2009; 75(3): 396.

53. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction Chemotherapy plus Radiation Compared with Surgery plus

Radiation in Patients with Advanced Laryngeal Cancer. N Engl J Med 1991; 324:1685-90.

54. Pointreau Y, Garaud P, Chapet S et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 2009; 101: 498–506.

55. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007; 357: 1695-1704.

56. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007; 357: 1705-1715.

57. Cohen EEW, Karrison T, Kocherginsky M, Huang CH, Agulnik M, Mittal BB et al. DeCIDE: A phase III randomized trial of docetaxel (D), cisplatin (P), 5-fluorouracil (F) (TPF) induction chemotherapy (IC) in patients with N2/N3 locally advanced squamous cell carcinoma of the head and neck (SCCHN). J. Clin. Oncol. 30(Suppl.), abstr 5500.

58. Haddad R. I., Rabinowits G., Tishler R. B., Adkins D., Khuri F. R., Clark J., et al. (2012). The PARADIGM trial: A phase III study comparing sequential therapy (ST) to concurrent chemoradiotherapy (CRT) in locally

advanced head and neck cancer (LANHC). J. Clin. Oncol.30(Suppl.), abstr 5501.

59. Jacobs C, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J ClinOncol 1992;10(2):257-63.

60. Catimel G, et al. Docetaxel (Taxotere): an active drug for the treatment of patients with advanced squamous cell carcinoma of the head and neck. EORTC Early Clinical Trials Group. Ann Oncol. 1994; 5(6):533-7.

61. Degardin M, et al. An EORTC-ECSG phase II study of vinorelbine in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol. 1998;9(10):1103-7.

62. Gibson MK, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. J ClinOncol. 2005;23(15):3562-7.

63. Herbst RS, et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. J ClinOncol. 2005; 23(24): 5578-87.

64. Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Co-operative Oncology Group study. J ClinOncol. 2005; 23(34): 8646-54.

65. Samlowski WE, et al. Evaluation of the combination of docetaxel/ carboplatin in patients with metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN): a Southwest Oncology Group Phase II study. Cancer Invest. 2007; 25(3):182-8.

66. Vermorken JB, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008 Sep 11; 359(11):1116-27.

67. Stewart JS, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck. J ClinOncol. 2009; 27(11):1864-71.

68. Grau JJ, Caballero M, Verger E, Monzó M, Blanch JL. Weekly paclitaxel for platin-resistant stage IV head and neck cancer patients. ActaOtolaryngol. 2009 Nov; 129(11):1294-9.

69. Martinez-Trufero J. Phase II study of capecitabine as palliative treatment for patients with recurrent and metastatic squamous head and neck cancer

after previous platinum-based treatment. Br J Cancer 2010; 102(12): 1687-91.

70. Molin Y, Fayette J. Current chemotherapies for recurrent/metastatic head and neck cancer. Anticancer Drugs 2011;22(7):621-5.

71. Joel Guigay, et al. Cetuximab, docetaxel, and cisplatin (TPEx) as first-line treatment in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Final results of phase II trial GORTEC 2008-03.Journal of Clinical Oncology, 2012 ASCO Annual Meeting Abstracts; 30(15): 5505.

72. Kowalski LP, Carvahlo AL. Natural history of untreated head and neck cancer. Eur J Cancer 2000;36:1032-7.

73. Carvalho AL, Salvajoli JV, Kowalski LP. A comparison of radiotherapy or radiochemotherapy with symptomatic treatment alone in patients with advanced head and neck carcinomas. Eur Arch Otorhinolaryngol 2000; 257:164-7.

74. Burns L, Chase D, Goodwin WJ Jr. Treatment of patients with stage IV cancer: Do the ends justify the means? Otolaryngol Head Neck Surg 1987; 97:8-14.

75. Erkal HS, Mendenhall WM, Amdur RJ, Villaret DB, Stringer SP. Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head and neck mucosal site treated with radiation therapy with palliative intent. RadiotherOncol 2001;59:319-21.

76. Lusinchi A, Bourhis J, Wibault P, Le Ridant AM, Eschwege F. Radiation therapy for head and neck cancers in the elderly. Int J RadiolBiolPhys 1990;18:819-23.

77. Isaacs JH Jr, Schnitman JR. Outcome of treatment of 160 patients with squamous cell carcinoma of the neck staged N3a. Head Neck 1990;12:483-7.

78. Wendt TG, Wustrow TP, Hartenstein RC, Rohloff R, Trott KR. Accelerated split course radiotherapy and simultaneous cis-platin and 5-fluorouracil chemotherapy with folinic acid enhancement for unresectable carcinoma of the head and neck. RadiotherOncol 1987; 10: 277-84.

79. Paris KJ, Spanos WJ, Lindberg RD, Jose B, Albrink F. Phase I-II study of multiple daily fractions for palliation of advanced head and neck malinancie. Int J RadiatOncolBiolPhys1993;25:657-60.

80. Minatel E, Gigante M, Franchin G, Gobitti C, Mascarin M, Bujor L, et al. Combined radiotherapy and bleomycin in patients with inoperable head

and neck cancer with unfavourable prognostic factors and severe symptoms. Oral Oncol 1998;34:119-22.

81. Stevens CM, et al. Retrospective study of palliative radiotherapy in newly diagnosed head and neck carcinoma. Int J RadiatOncolBiol Phys. 2011; 81(4): 958-63.

82. Porceddu SV, et al. Hypofractionated radiotherapy for the palliation of advanced head and neck cancer in patients unsuitable for curative treatment--"Hypo Trial". RadiotherOncol. 2007; 85(3):456-62.

83. Abrahim Al-Mamgani, Lisa Tans, Peter H. E. Van Rooij, IngeNoever, Robert J. Baatenburg De Jong and Peter C. Levendag. Hypofractionated radiotherapy denoted as the ‘‘Christie scheme’’: An effective means of palliating patients with head and neck cancers not suitable for curative treatment. ActaOncologica, 2009; 48: 562-70.

84. Ghoshal S, Patel F, Mudgil N, Bansal M, Sharma S. Palliative radiotherapy in locally advanced head and neckcancer: A prospective trial. Indian J Palliat Care 2004;10:1923.

85. Corry J, Peters LJ, Costa ID, Milner AD, Fawns H, Rischin D, et al. The ‘QUAD SHOT’—A phase II study of palliative radiotherapy for incurable head and neck cancer. RadiotherOncol 2005;77:137-42.

86. Kancherla KN, et al. The Role of Split-course Hypofractionated Palliative Radiotherapy in Head and Neck Cancer. Clinical Oncology 2011; 23: 141-48.

87. Fletcher GH. Elective irradiation of subclinical disease in cancers of the head and neck. Cancer 1972; 29(6):1450–1454.

88. Ogura JH, Biller HF, Wette R. Elective neck dissection for pharyngeal and laryngeal cancers. An evaluation. Ann OtolRhinolLaryngol 1971; 80(5):646–650.

APPENDIX – I

TABLE No	DESCRIPTION
1	Age Distribution
2	Sex Distribution
3	Performance Status
4	Stage Grouping
5	Stage Distribution
6	Symptoms at Presentation
7	Sites of Primary Tumour
8	Oral Cavity Sub-sites
9	Oropharyngeal Sub-sites
10	Hypopharyngeal Sub-sites
11	Reason for Palliative Policy
12	Symptom Change after First Course
13	Toxicities out of First Course
14	Response out of First Course
15	Symptom Relief at First Follow Up
16	Toxicities at First Follow Up
17	Response at First Follow Up
18	Global Health Status
19	Functional Scales
20	Literature on Palliative Radiotherapy

APPENDIX – II

FIGURE No	DESCRIPTION
1	Isoeffect relationship
2	Age Distribution
3	Sex Distribution
4	Performance Status
5	Stage Grouping
6	Stage Distribution
7	Symptoms at Presentation
8	Site of Primary Tumour
9	Oral Cavity Sub-sites
10	Oropharyngeal Sub-sites
11	Hypopharyngeal Sub-sites
12	Reason for Palliative Policy
13	Symptom Change after First Course
14	Toxicities after First Course
15	Response at First Course
16	Symptom Change at First Follow Up
17	Toxicities at First Follow Up
18	Response at First Follow Up
19	Global Health Status
20	Functional Scales
21	Symptom Scales

ANNEXURES

ANNEXURE - I

RTOG CTCAE V4.03

Grade	0	1	2	3	4
Skin	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucous Membrane	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
Pharynx &Esophagus	No change over baseline	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet	Moderate dysphagia or odynophagia/ may require narcotic analgesics/ may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss(>15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyper alimentation	Complete obstruction, ulceration, perforation, fistula

SALIVARY GLAND	No change over baseline	Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste such as metallic taste/ these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness/ thick, sticky saliva/ markedly altered taste		Acute salivary gland necrosis
Laryngitis	No change over baseline	Mild or intermittent hoarseness/ cough not requiring antitussive/ erythema of mucosa	Persistent hoarseness but able to vocalize/ referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/ antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/ confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary

ANNEXURE - II

Information to Participants

Title: - "SPLIT-COURSE HYPOFRACTIONATED RADIOTHERAPY FOR PALLIATION OF ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA"

PrincipalInvestigator: Dr. Vishal D Manik

Name of Participant:

Site: Department of Radiotherapy, Madras Medical College & RGGGH, Chennai-3

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

Head & neck cancer are one of the most common malignancy noted in our daily practice. Due to the insidious nature of the disease, many cases are unnoticed until they progress to advanced stage. Some of such advanced cases can be treated aggressively if the patient's general condition permits or if patient is young, without co-morbidities. However those with poor general condition, depleted nutritional status, existing co-morbidities or very advanced stage where curative intent is unrealistic, the usual treatment plan is palliation. Palliation is given either in form of radiotherapy, chemotherapy or best supportive care.Radiotherapy is the best modality available for palliation in head & neck malignancies. Limited evidence & guidelines are available regarding optimal dosage and fractionation in palliative setting for head & neck cancer sites. We want to test the efficacy of an altered treatment schedule in this disease.

We have obtained permission from the Institutional Ethics Committee.

The study design: Single arm Phase II Prospective study

Study Procedures: The study involves evaluation of Advanced Head & Neck Squamous cell carcinoma treated with split-course hypofractionated therapy forwhich we will need, Chest X-ray, CECT Head & Neck, before & after treatment as part of standard protocol for any other patient receiving radiotherapy. At each visit, the study physician will examine you. Some blood tests will be carried out at first & second visit before each radiation course. 5ml of blood will be collected each time. Blood collection involves prick with a needle and syringe. These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you. In addition, if you notice any physical or mental change(s), you must contact the persons listed at the end of the document.

You may have to come to the hospital for examination and investigations apart from your scheduled visits, if required.

Possible risks to you – None greater than standard patients receiving radiotherapy

Possible benefits to you -

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator Signature of Participant

Date Date

ANNEXURE - III

INFORMED CONSENT FORM

TITLE OF THE STUDY: "SPLIT-COURSE HYPOFRACTIONATED RADIOTHERAPY FOR PALLIATION OF ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA"

NAME OF THE PARTICIPANT:

NAME OF THE PRINCIPAL (Co – Investigator) : DR. Vishal D Manik

NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

I,_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in "SPLIT-COURSE HYPOFRACTIONATED RADIOTHERAPY FOR PALLIATION OF ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA"

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me and about the nature of the study.
3. I have been explained about my rights and responsibilities by the investigator.
4. I have informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.
5. I have been advised about the risks associated with my participation in this study.*****
6. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms. *****
7. I have not participated in any research study within the past 12 month(s). *****
8. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *****
9. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *****
10. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
11. I understand that my identity will be kept confidential if my data are publicly presented
12. I have had my questions answered to my satisfaction.
13. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator.

By signing this consent form I attest that the information given in this document has been clearly explained and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant

Name _____ Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____ Date_____

ANNEXURE - IV

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவமனைக்கு வரும் புற்று நோயாளிகளிடம்கதிர்வீச்சுசிகிச்சைப் பற்றிய ஆராய்ச்சி.

தலை மற்றும் கழுத்து பகுதியில் முற்றிய புற்றுநோய்க்கு பல வகையான கதிர்வீச்சு சிகிச்சை முறைகள் உள்ளன. அவற்றுள் குணப்படுத்த முடியாத மிகவும் முற்றிய புற்றுநோய்க்கு முதலில் ஒரு வாரத்திற்கு தீவிர கதிர்வீச்சு சிகிச்சை அளித்த பிறகு இரண்டு வாரங்கள் கழித்து மீண்டும் ஒரு வாரத்திற்கு தீவிர கதிர்வீச்சு சிகிச்சை அளித்து புற்றுநோயின் தீவிரத்தை குறைப்பது பற்றி ஆராய்வது இந்த ஆராய்ச்சியின் நோக்கம்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க விரும்புகிறோம். இந்த ஆராய்ச்சியில் தீவிர கதிர்வீச்சு சிகிச்சை அளித்து சில சிறப்பு பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். இதனால் தங்கள் நோயின்ஆய்வறிக்கையோசிகிச்சையோ பாதிப்பு எற்படாது என்பதை தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின்போதோ தங்களின் பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின்முடிவுகளையும்நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

_____	_____
ஆராய்ச்சியாளர் கையொப்பம்	பங்கேற்பாளர் கையொப்பம்
தேதி:	தேதி:

ANNEXURE - V

ஆராய்ச்சி ஒப்புதல் கடிதம்

தலை மற்றும் கழுத்து பகுதியில் மிகவும் முற்றிய புற்றுநோய்க்கு ஒரு வாரத்திற்கு தீவிர கதிர்வீச்சு சிகிச்சை அளித்த பிறகு இரண்டு வாரங்கள் கழித்து மீண்டும் ஒரு வாரத்திற்கு தீவிர கதிர்வீச்சு சிகிச்சை அளித்து செய்யப்படும் ஆய்வு.

பெயர்: தேதி:

வயது: உள்/புற நோயாளி எண்:

பால்: ஆராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின்விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு விளக்கப்பட்டன.

எனக்கு விளக்கப்பட்ட விவரங்களை நான் புரிந்துகொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

எனக்கு புற்றுநோய் இருக்கும் பகுதியில் கதிர்வீச்சு சிகிச்சை செய்து கொள்ள சம்மதம்.

இந்த ஆராய்ச்சியில் பிறரின்நிர்ப்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் பங்கு பெறுகிறேன்.இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

நான் தலை மற்றும் கழுத்து பகுதியில் முற்றிய புற்று நோய் குறித்த இந்த ஆய்வுக்கான விவரங்கள் கொண்ட தகவல் தாளைப்பெற்றுக்கொண்டேன்.

எனக்கு இந்த ஆராய்ச்சியில் தீவிர கதிர்வீச்சு சிகிச்சை பெற்றுக் கொள்ள சம்மதம்.

இந்த ஆராய்ச்சியினால் ஏற்படும் நன்மைகளையும், சில பக்கவிளைவுகளையும் பற்றி தெளிவாக மருத்துவர் மூலம் தெரிந்து கொண்டேன்.

நான் என்னுடைய சுயநினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதம் தெரிவிக்கிறேன்.

கையொப்பம்

ANNEXURE - VI

TAMIL

EORTC QLQ - C30 (version 3)

நாங்கள் உங்களையும், உங்கள் ஆரோக்கியத்தையும் பற்றி சில விஷயங்களை அறிய ஆர்வமாய் உள்ளோம். தயவு செய்து எல்லாக் கேள்விகளுக்கும் நீங்களே பதில் தாருங்கள். உங்களுக்கு உச்ச அளவில் பொருந்தும் எண்ணைச் சுற்றி வட்டமிடவும். "சரியான" அல்லது "தவறான" பதில்கள் கிடையாது. நீங்கள் தரும் விபரம் கண்டிப்பாக ரகசியமாக இருக்கும்.

தயவு செய்து உங்கள் பெயரின் முதல் எழுத்துகளை இட்டு நிரப்பவும். _____

உங்களது பிறந்த தேதி (நாள், மாதம், வருடம்) _____

இன்றைய தேதி _____

		இல்லவே இல்லை	ஒரு சிறிது	கணிசமாக	மிக அதிக அளவு
1	நீங்கள் ஒரு கனமான கூடைச் சாக்குப்பை அல்லது ஒரு கைப் பெட்டியைத் தூக்குவது போன்ற கடினமான வேலைகள் செய்கையில் ஏதாவது தொல்லை அனுபவிக்கிறீர்களா?	1	2	3	4
2	நீண்ட நேர நடை எடுக்கையில் நீங்கள் ஏதாவது தொல்லை கொண்டுள்ளீர்களா?	1	2	3	4
3	வீட்டுக்கு வெளியில் சின்ன நடை எடுக்கையில் நீங்கள் ஏதேனும் தொல்லை கொண்டுள்ளீர்களா?	1	2	3	4
4	பகலில் படுக்கை மீது அல்லது ஒரு நாற்காலியில் இருக்கும்படி நீங்கள் தேவையை உணர்கிறீர்களா?	1	2	3	4
5	நீங்கள் சாப்பிட, உடுத்த, குளிக்க அல்லது கழிப்பிடத்தைப் பயன்படுத்த உதவி தேவைப்படுகிறதா?	1	2	3	4
	கடந்த வாரத்தின் போது:				
6	நீங்கள் உங்கள் வேலையையோ அல்லது மற்ற ஒவ்வொரு நாள் நடவடிக்கைகளையோ செய்கையில் வரம்புக்குள் இருந்தீர்களா?	1	2	3	4
7	நீங்கள் உங்களது பிடித்த பொழுது போக்குகள் அல்லது பிற ஓய்வு நேர நடவடிக்கைகளைத் தொடரும் போது வரம்புக்குள் இருந்தீர்களா?	1	2	3	4
8	நீங்கள் மூச்சுத் திணறலுடன் இருந்தீர்களா?	1	2	3	4
9	நீங்கள் உடலில் வலி கொண்டிருந்தீர்களா?	1	2	3	4
10	நீங்கள் ஓய்வு எடுக்கத் தேவைப்பட்டதா?	1	2	3	4
11	நீங்கள் தூங்குவதில் தொல்லை கொண்டிருந்தீர்களா?	1	2	3	4
12	நீங்கள் பலவீனமாக உணர்ந்து இருந்தீர்களா?	1	2	3	4

தயவு செய்து அடுத்த பக்கத்திற்குப் போகவும்

	கடந்த வாரத்தின் போது:	இல்லவே இல்லை	ஒரு சிறிது	கணிசமாக	மிக அதிக அளவு
13	நீங்கள் பசிஎடுப்பது இல்லாது இருந்தீர்களா?	1	2	3	4
14	நீங்கள் குமட்டுவது போல உணர்ந்தீர்களா?	1	2	3	4
15	நீங்கள் வாந்திஎடுத்துள்ளீர்களா?	1	2	3	4
16	நீங்கள் மலச்சிக்கல் கொண்டிருந்தீர்களா?	1	2	3	4
17	நீங்கள் தொடர்ந்து வயிற்றுப் போக்கு கொண்டிருந்தீர்களா?	1	2	3	4
18	நீங்கள் களைப்படைந்தீர்களா?	1	2	3	4
19	வலி உங்களது தினசரி நடவடிக்கைகளில் இடையூறு செய்ததா?	1	2	3	4
20	நீங்கள் ஒரு செய்தித்தாள் வாசிப்பது அல்லது தொலைக்காட்சி பார்ப்பது போன்ற விஷயங்கள் மேல் கவனம் செலுத்துவதில் கஷ்டம் கொண்டிருந்தீர்களா?	1	2	3	4
21	நீங்கள் பதற்றமான இருக்கத்தை உணர்ந்தீர்களா?	1	2	3	4
22	நீங்கள் கவலைப்பட்டீர்களா?	1	2	3	4
23	நீங்கள் எரிச்சல் பட்டீர்களா?	1	2	3	4
24	நீங்கள் மன அழுத்தம் உணர்ந்தீர்களா?	1	2	3	4
25	நீங்கள் பொருட்களை ஞாபகம் கொள்வதில் கஷ்டப்பட்டிருந்தீர்களா?	1	2	3	4
26	உங்கள் உடல் நிலைமை அல்லது மருத்துவச் சிகிச்சை உங்களது குடும்ப வாழ்க்கையோடு குறுக்கிட்டுப் பாதித்து இருக்கிறதா?	1	2	3	4
27	உங்கள் உடல் நிலைமை அல்லது மருத்துவச் சிகிச்சை உங்களது சமூக நடவடிக்கைகளோடு குறுக்கிட்டுப் பாதித்து இருக்கிறதா?	1	2	3	4
28	உங்கள் உடல் நிலைமை அல்லது மருத்துவச் சிகிச்சை உங்களுக்கு நிதிக் கஷ்டங்களை உண்டாக்கி உள்ளதா?	1	2	3	4

பின்வரும் கேள்விகளுக்கு 1லிருந்து 7 முடிய உள்ள எண்களில், உங்களது நிலைமைக்கு உச்ச அளவில் பொருந்தும் எண்ணைச் சுற்றி தயவு செய்து வட்டமிடவும்.

29 கடந்த வாரத்தின் போது, பொதுவாக, உங்களுடைய ஆரோக்கியத்தை நீங்கள் எவ்வாறு மதிப்பீடு செய்வீர்கள்?

1 2 3 4 5 6 7

(மிக மோசம்) (பிரமாதம்)

30 கடந்த வாரத்தின் போது, பொதுவாக, உங்களுடைய வாழ்க்கைத் தரத்தை நீங்கள் எவ்வாறு மதிப்பீடு செய்வீர்கள்?

1 2 3 4 5 6 7

(மிக மோசம்) (பிரமாதம்)

ANNEXURE - VII

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Vishal D Manik,
PG in Radio Therapy,
Department of Radio Therapy,
Madras Medical College, Chennai-3.

Dear Dr. Vishal D Manik,

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"Split-Course Hypofractionated Radiotherapy For Palliation Of Advanced Head And Neck Squamous Cell Carcinoma"** No.05032014

The following members of Ethics Committee were present in the meeting held on 11.03.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr. C. Rajendran, M.D.	-- Chairperson
2.	Prof. Kalaiselvi, MD Vice-Principal, MMC, Ch-3	-- Member Secretary
3.	Prof. Nandhini, M.D. Inst. of Pharmacology, MMC, Ch-3.	-- Member
4.	Prof. Bhavani Shankar, M.S. Prof & HOD of General Surgery, MMC, Ch-3.	-- Member
5.	Prof. V. Padmavathi, M.D. I/c Director of Pathology, MMC, Ch-3.	-- Member
6.	Thiru. S. Govindasamy, BABL	-- Lawyer
7.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

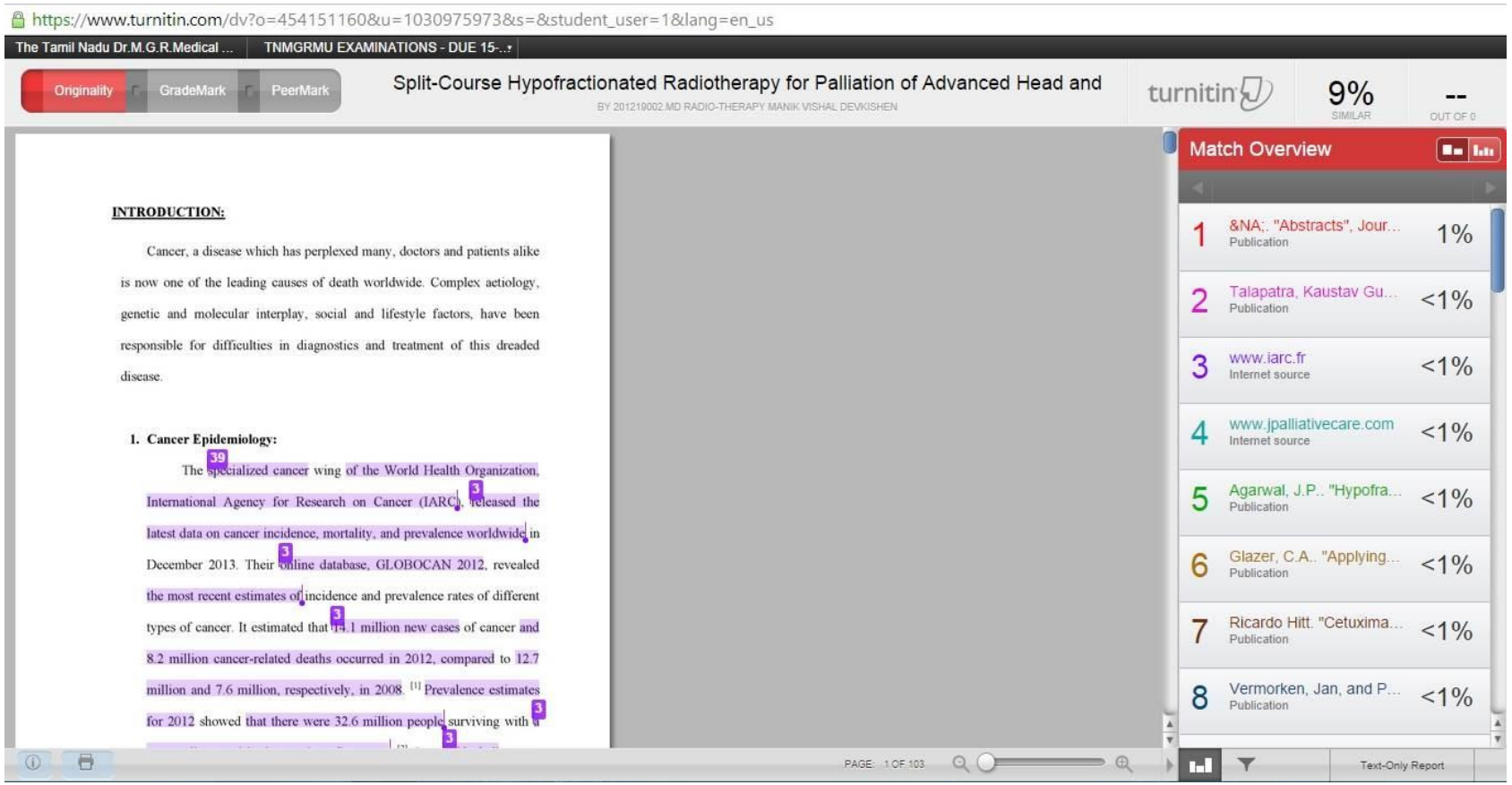
Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

13/3/14

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

Member Secretary, Ethics Committee



ANNEXURE - VIII

ANNEXURE IX

Split-Course Hypofractionated Radiotherapy for Palliation of Advanced Head and Neck Squamous Cell Carcinoma

ORIGINALITY REPORT

9%	3%	8%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	&NA;. "Abstracts", Journal of Thoracic Oncology, 09/2009 Publication	1%
2	Talapatra, Kaustav Gupta, Tejpal Agarwal. "Palliative radiotherapy in head and neck cancers: Evidence based review.(Review Article)", Indian Journal of Palliative Care, July-Dec 2006 Issue Publication	<1%
3	www.iarc.fr Internet Source	<1%
4	www.jpalliativecare.com Internet Source	<1%
5	Agarwal, J.P.. "Hypofractionated, palliative radiotherapy for advanced head and neck cancer", Radiotherapy and Oncology, 200810 Publication	<1%
6	Glazer, C.A.. "Applying the molecular biology and epigenetics of head and neck cancer in	<1%